Cognitive Control of Emotional Information in Schizophrenia: Understanding the Mechanisms of Social Functioning Impairments

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Abstract

Social functioning impairments are a core, debilitating, and treatment refractory feature of schizophrenia. The mechanisms contributing to these impairments are unknown. Cognitive control mechanisms, mediated by the lateral prefrontal cortex (LPFC), are known to influence response to interpersonal stressors in healthy individuals, thus impairments in these processes may contribute to social deficits. Deficits in cognitive control and lateral prefrontal abnormalities are well-documented in schizophrenia, but the relationship between these deficits and social interactions has received limited attention in the literature. The current dissertation presents a systematic examination of the contribution of the behavioral and neural mechanisms of cognitive control to social functioning impairments in schizophrenia. Three papers are presented.

Paper #1 demonstrates that individual differences in social anhedonia - an established personality risk factor for schizophrenia and a core negative symptom of the disease - relate to social impairments and that this relationship is partially mediated by self-reported cognitive control. Using surface based morphometry methods, paper #2 establishes a relationship between decreased cortical thickness in the LPFC (superior frontal gyrus) and decreased role functioning across a sample of schizophrenia and healthy participants; moreover, cognitive control fully mediated this relationship. Paper #3 combined functional MRI and experience sampling methods to established a relationship between lateral prefrontal dysfunction during cognitive control, specifically of emotional information, and daily social experiences in schizophrenia.

Schizophrenia participants showed reduced LPFC activation during cognitive control of negative emotional information. Moreover, the extent of LPFC activation during cognitive control of negative emotional information predicted symptom exacerbation and daily social experiences.

Taken together, the three papers of this dissertation clearly establish impaired cognitive control as one of the mechanisms underlying functional impairment in schizophrenia, demonstrating a direct link between a putative biomarker for schizophrenia (LPFC dysfunction), and one of the core behavioral characteristics of the illness - social impairments. This dissertation addresses important gaps in our understanding of the relationship between the neurofunctional and neuroanatomical mechanisms of cognitive control, and real-world functioning. These findings suggest that cognitive control, specifically of emotional information, could be a potential target for intervention to ameliorate social deficits in schizophrenia.

Table of Contents

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Background and Introduction

Pervasive and disabling social functioning impairments are a central feature of schizophrenia (Couture, Penn, & Roberts, 2006). These impairments are observed across schizophrenia-spectrum disorders and high-risk populations (Hans, Auerbach, Asarnowm, Styr, & Marcus, 2000), are present premorbidly (Davidson, et al., 1999), and are known to impact the full gamut of important mental health outcomes. Levels of social support and social competence predict illness onset (DeVylder & Gearing, in press), likelihood for future psychotic episodes (Alvarez-Jimenez, et al., 2011), symptom severity and remission (Corrigan & Phelan, 2004; Norman, et al., 2005), relapse (Hooley, 2010), recovery (Hendryx, Green, & Perrin, 2009) and quality of life (Bellack, Morrison, Wixted, & Mueser, 1990). Given the extensive impact of social deficits on illness trajectory and well-being in schizophrenia, research has increasingly been directed toward understanding the factors that contribute to social functioning impairments. Neurocognition is one such factor.

Neurocognitive deficits are well-documented in schizophrenia. These deficits are present regardless of illness stage (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009), are seen on neuropsychological measures assessing multiple domains including verbal fluency, memory, attention, processing speed, and executive functioning (Heinrichs & Zakzanis, 1998), and are consistently associated with neural abnormalities in frontal and temporal lobe activation (Barch, 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Moreover, impairments in these domains relate to increased symptom severity and poor social functioning (Addington & Addington, 2000; Green, Kern, & Heaton, 2004), providing a clear link between putative neurocognitive endophenotypes of the disorder (Snitz, MacDonald, & Carter, 2006) and their clinical/social manifestations in patients' daily lives. However, how these neurocognitive

impairments impact social functioning remains unclear. The myriad of seemingly unique and disparate deficits across multiple domains limits our ability to isolate the specific mechanistic pathways to social impairment. Standardized tasks often involve multiple cognitive processes, thus the exact nature of the deficit and how it might relate to functioning is unclear. Although it is possible that schizophrenia can be characterized by multiple discrete neurocognitive deficits, each exerting a unique impact on social functioning, a more parsimonious account of the pathway from the pathophysiological mechanisms of neurocognitive deficits to social functioning impairments is desirable. One proposal is that the multiple neurocognitive deficits and their accompanying neural abnormalities can be explained in the context of a fundamental and domain-general impairment in cognitive control that confers impairments on higher-level processes (Lesh, Niendam, Minzenberg, & Carter, 2011).

Cognitive control, also termed attentional, effortful, or executive control, can be operationalized as the inhibitory and facilitatory functions necessary to maintain task-relevant processing and goal-oriented behavior; that is, inhibiting irrelevant information and facilitating the relevant (Banich, et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000). As such cognitive control is a key component to the successful management and implementation of the complex mental processes required in day-to-day life; impairments in cognitive control processes are likely to impact daily life functioning. Behavioral and cognitive neuroscience research has consistently documented cognitive control impairments in schizophrenia (Mesholam-Gately, et al., 2009; Minzenberg, et al., 2009), leading to the proposal that it may be a biomarker for the illness (Woodward, et al., 2009). However, the precise nature of the relationship between the neural and behavioral components of cognitive control and social impairments remains unclear. Determining the nature of this relationship would contribute to our understanding of how the

neurobiological substrates of schizophrenia results in the clinical manifestation of the illness, and could aid the development of effective interventions and the consequential improvement of functional outcome.

This dissertation presents a systematic investigation of the contribution of cognitive control to social impairments in schizophrenia at behavioral and neural levels, with specific focus on understanding the role of the lateral prefrontal cortex in cognitive control processes, particularly the cognitive control of emotional information. Below I present a targeted review of the relevant literature, followed by a statement of the specific research questions addressed in this dissertation. Three papers addressing these research questions are then presented followed by a summary of implications and concluding thoughts.

The Lateral Prefrontal Cortex and Cognitive Control Network

Cognitive neuroscience studies in healthy individuals have identified a cingulo-frontal-parietal cognitive control network involving the lateral prefrontal cortex (LPFC), particularly the dorsolateral PFC (DLPFC), the anterior cingulate cortex (ACC), and parietal regions (Miller & Cohen, 2001). The DLPFC is thought to maintain rules and goals relevant to the current task, and, in the presence of conflicting information that might prompt prepotent but inappropriate responses, exerts "top down" control to direct neural processing toward the current goal (Miller, 2000; Miller & Cohen, 2001). The ACC is thought to detect the presence of response conflict and signal the DLPFC when top down control is needed to maintain task-relevant processing (Botvinick, Braver, Barch, Carter, & Cohen, 2001; MacDonald, et al., 2000), and parietal regions are involved in shifting and orienting attention towards task-appropriate stimuli (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Posner & Petersen, 1990). Thus the LPFC plays a central role in the inhibition of task-irrelevant responses and facilitation of continued task-

relevant processing; that is, orchestrating brain processing toward desired responses and away from prepotent but incorrect ones (Miller & Cohen, 2001). It is perhaps not surprising then that damage to lateral prefrontal regions leads to impairments in inhibitory processes (Miller, 2000) and affects skills of daily living (Burgess, Veitch, de Lacy Costello, & Shallice, 2000). Given its key role in cognitive control processes this dissertation focuses on the role of LPFC abnormalities in schizophrenia, and the contribution of the LPFC mediated cognitive control processes to the functional impairments of the illness.

LPFC Abnormalities in Schizophrenia

LPFC dysfunction is a well established neural impairment in schizophrenia. Functional neuroimaging studies predominantly report reduced activation compared to healthy individuals on a range of executive functioning tasks that also tap cognitive control, including the Wisconsin Card Sorting Task (WCST; Ragland, et al., 1998) and the N-Back (Perlstein, Carter, Noll, & Cohen, 2001), as well as tasks specifically designed to assess cognitive control such as the AX-CPT (MacDonald, et al., 2005), the Multi-Source Interference Task (Harrison, et al., 2007) and the Simon task (Snitz, et al., 2005) (see Glahn, et al., 2005; Minzenberg, et al., 2009 for reviews). However, reports of hypoactivation are not consistent across the literature (Callicott, et al., 2000; Callicott, et al., 2003), thought to be partly due to differential activation-load curves (i.e. relationship between task difficulty and LPFC activation) between healthy and schizophrenia populations (Callicott, et al., 2003), prompting the "inefficiency" hypothesis of LPFC dysfunction in schizophrenia (Potkin, et al., 2009). Importantly, abnormal LPFC activation has been observed in clinical high-risk (Fusar-Poli, et al., 2010) and genetic high-risk samples (Becker, Kerns, MacDonald, & Carter, 2008), suggesting that LPFC dysfunction may be associated with clinical and genetic liability for schizophrenia.

Structural neuroimaging studies also consistently report abnormalities in the LPFC in schizophrenia, suggesting that the observed neurofunctional abnormalities in the cognitive control network may be rooted in neuroanatomical abnormalities. A wealth of studies using voxel based morphometry (VBM), a method for detecting group differences in the density or volume of brain matter (Ashburner & Friston, 2000), have demonstrated reduced grey matter volume (GMV) in the LPFC (e.g. Ananth, et al., 2002; Antonova, et al., 2005; Glahn, et al., 2008; Kawasaki, et al., 2004; Marcelis, et al., 2003; Meda, et al., 2008; Narr, et al., 2005; Sigmundsson, et al., 2001). In a meta-analysis of VBM studies in schizophrenia Honea and colleagues (2005) found that 66% of VBM studies reported findings of reduced GMV in LPFC regions (middle and inferior frontal gyri), with the left inferior frontal gyrus reported most frequently. Similarly, studies using surface based morphometry (SBM), a method for detecting group differences in cortical surface characteristics including cortical thickness, surface area, cortical folding, and gyral complexity, have reported a pattern of cortical surface abnormalities in lateral prefrontal regions, including reduced cortical thickness (Janssen, et al., 2009; Kuperberg, et al., 2003; Oertel-Knöchel, et al., 2012; Venkatasubramanian, Jayakumar, Gangadhar, & Keshavan, 2008; Voets, et al., 2008), and abnormalities in cortical folding/gyral complexity (Bonnici, et al., 2007; Cachia, et al., 2008; Narr, et al., 2004; Wisco, et al., 2007). Moreover, both neuroanatomical and neurofunctional abnormalities in the LPFC are present in genetic high risk (Cannon, et al., 2002; Oertel-Knöchel, et al., 2012) and clinical high risk populations (Fusar-Poli, Borgwardt, et al., 2011), and predict conversion to psychosis (Harris, et al., 2007), further supporting the proposal that LPFC abnormalities are part of the clinical and genetic liability for schizophrenia.

Indeed, LPFC abnormalities are so well-documented in individuals with schizophrenia (Glahn, et al., 2008; Minzenberg, et al., 2009) and individuals at genetic and clinic high risk (Fusar-Poli, Borgwardt, et al., 2011) that LPFC dysfunction has been proposed as a biomarker for the illness (Lesh, et al., 2011; Wood, et al., 2008; Woodward, et al., 2009). However, without directly tying LPFC dysfunction to the core characteristics of the disorder, including pervasive functional difficulties, its usefulness as a biomarker remains unclear. A primary aim of this dissertation is to directly link LPFC abnormalities, specifically in the context of cognitive control processes, to the functional impairments in schizophrenia.

Linking LPFC Abnormalities to the Core Characteristics of Illness

Research has begun to examine relationships between lateral prefrontal abnormalities and the clinical and behavioral aspects of schizophrenia. Converging evidence from structural neuroimaging studies suggest a relationship between LPFC abnormalities, cognitive control impairments, and functioning. Reduced cortical thickness/GMV relates to decreased global functioning (Chemerinski, Nopoulos, Crespo-Facorro, Andreasen, & Magnotta, 2002; Prasad, Sahni, Rohm, & Keshavan, 2005), as well as poor performance on behavioral tasks tapping cognitive control, including the WCST (Ho, et al., 2003; Seidman, et al., 1994), the continuous performance task (Salgado-Pineda, et al., 2004), the N-back (Zierhut, et al., in press), the Controlled Oral Word Association Test (COWAT; Minatogawa-Chang, et al., 2009) and category verbal fluency (Takizawa, et al., 2008) - tasks that are known to predict functional outcome (Addington & Addington, 2000; Green, 1998; Milev, Beng-Choon Ho, Arndt, & Andreasen, 2005). Considered together these findings suggest that structural abnormalities in the LPFC affect functioning through cognitive control processes; that is, cognitive control processes may mediate the relationship between neuroanatomical abnormalities in the LPFC and functional

impairments. However, to our knowledge no studies have examined this putative mediation model directly.

Evidence from functional neuroimaging studies also suggests that LPFC dysfunction during cognitive control relates to core characteristics of schizophrenia. To date, studies have primarily focused on the relationship between the LPFC and symptoms. LPFC dysfunction during cognitive control tasks relates to increased negative (Goghari, Sponheim, & MacDonald, 2010; van Veelen, Vink, Ramsey, & Kahn, 2010), positive (Menon, Anagnoson, Mathalon, Glover, & Pfefferbaum, 2001), disorganized (MacDonald, et al., 2005; Perlstein, et al., 2001) symptoms, and normalization of LPFC activity relates to decreased symptoms (Edwards, Barch, & Braver, 2010; Fusar-Poli, Broome, et al., 2011) and better treatment response (Kumari, et al., 2009). Collectively, these findings clearly indicate a direct link between LPFC pathophysiology and symptomatology in schizophrenia. However, to our knowledge only two studies have reported a relationship between LPFC activity and functional outcome. Both demonstrated reduced LPFC connectivity within fronto-parietal networks during cognitive control related to impairments on global measures of functioning (Sanz, et al., 2009; Yoon, et al., 2008). However, further investigation into the relationship between LPFC deficits and social functioning is warranted; global measures of functioning do not delineate between social contexts and role functioning (i.e. work/school), and by providing one aggregate score as a summary of an individual's behavior may miss potentially important fluctuations in social behavior. Thus the specific role of the LPFC mediated cognitive control in social contexts remains unknown.

Cognitive Control of Emotional Information and Social Functioning

Given the inherently affective nature of social interactions, it is possible that the scarcity of studies reporting a direct link between LPFC function and social deficits is because tasks

traditionally used to asses LPFC function do not typically measure cognitive control processes in relation to socially relevant information; for example, emotional information. Social interactions, particularly interpersonal conflicts, can be emotionally challenging and require regulation of negative affect and behavior for successful resolution (Arriaga & Rusbult, 1998; Lopes, et al., 2011). Thus, deficits in the cognitive control of emotional information could adversely affect response to interpersonal stressors and consequently social functioning. Therefore, tasks assessing the interaction between LPFC mediated cognitive control and emotional information may be a more accurate reflection of the inhibitory demands of real-world social contexts, and may provide a more direct measure of the process through which impaired cognitive control impacts social functioning.

Consistent with this proposal, evidence suggests that LPFC mediated control of emotional information underlies the facilitation and regulation of emotions, as well as their translation into goal-directed behavior (Ochsner & Gross, 2005). Moreover, functional neuroimaging studies in healthy individuals suggest LPFC function impacts response to interpersonal stressors. The less that individuals recruit LPFC regulatory mechanisms, the less self-regulation they report in everyday life: Lower LPFC activity during the "Cyberball" social exclusion task, in which participants play a virtual ball tossing game with two other players who eventually exclude them from the game (Williams & Jarvis, 2006), predicts higher self-reported distress as a consequence of that exclusion (Eisenberger, Lieberman, & Williams, 2003), and daily levels of social support (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). Similarly, lower LPFC activity when viewing negative facial expressions of one's partner predicts increased negative mood and maladaptive behavior following conflict with that partner (Hooker, Gyurak, Verosky, Miyakawa, & Ayduk, 2010). Thus, impairments in the ability to

engage cognitive control mechanisms in the face of a social/emotional stressor could result in difficulties in social interactions.

Behavioral studies suggest that cognitive control of emotional information is impaired in schizophrenia. Impaired cognitive control of irrelevant emotional information contributes to negative affective pictures exerting inappropriate influence on social judgments of trustworthiness (Hooker, et al., 2011), and subliminal affective face primes negatively biasing valence judgments of neutral Chinese characters (Suslow, Roestel, & Arolt, 2003). Moreover, impairments in the inhibition of irrelevant negative affective information has been observed in individuals with high social anhedonia (SA) - a traitlike disinterest in social interactions and a personality risk factor for developing schizophrenia - suggesting that it may be part of the liability for the disorder (Tully, Lincoln, & Hooker, 2012). However, studies examining the neural mechanisms underlying these impairments are limited. Failure to recruit lateral prefrontal regions when viewing socially accepting and rejecting faces has been shown to predict maladaptive responses to interpersonal conflict in high SA individuals (Hooker, Benson-Leigh, Gyurak, Tully, & Lincoln, under review) but this has yet to be examined in individuals with schizophrenia.

Research Questions

The current dissertation consists of a systematic investigation of the contribution of cognitive control deficits to social functioning impairments in schizophrenia at behavioral and neural levels. Given that LPFC mediated cognitive control impairments are well-documented in schizophrenia and considered a putative biomarker for the illness, understanding the way LPFC deficits impact social functioning impairments could further our understanding of how the

underlying neurobiological substrates of the disorder are expressed in the clinical and social aspects of the illness. First, this dissertation seeks to establish a connection between cognitive control mechanisms and social functioning. Second, this dissertation seeks to meaningfully connect neural indicators, both structural and functional, of cognitive control processes to measures of social functioning. If LPFC deficits during cognitive control, specifically cognitive control of emotion, predict social impairments, this furthers our understanding of the development and maintenance of social impairments and provides possible targets for interventions to ameliorate them.

In this dissertation, I provide data to address the following questions:

Question #1: *Is cognitive control a contributing factor to individual differences in social functioning? Do individual differences in cognitive control mediate the relationship between social anhedonia, a risk factor for schizophrenia, and social functioning?*

Paper #1: Tully, L. M., Lincoln, S. H., & Hooker, C. I. (under review) Attentional control mediates the relationship between social anhedonia and social impairment.

Paper #1 use self-report methods to directly test the hypothesis that cognitive control abilities mediate the relationship between social anhedonia and social impairments. We use the Attentional Control Scale (Derryberry & Reed, 2002) to measure self-reported cognitive control abilities, thus we refer to cognitive control in this paper as attentional control.

Question #2: *Do neuroanatomical abnormalities in lateral prefrontal regions relate to social functioning impairments in schizophrenia? Do cognitive control abilities mediate the relationship between lateral prefrontal abnormalities and social functioning?*

Paper #2: Tully, L. M., Lincoln, S. H., Liyanage-Don, N., & Hooker, C. I. (in preparation) Impaired cognitive control mediates the relationship between abnormalities in cortical thickness of the superior frontal gyrus and role functioning in schizophrenia.

Paper #2 uses structural magnetic resonance imaging (MRI) to directly test the hypothesis that LPFC structural abnormalities impact social and role functioning via impaired cognitive control.

Question #3: *Do schizophrenia participants show LPFC dysfunction during cognitive control of emotional information compared to healthy participants? Does LPFC activity during cognitive control of emotional information predict daily social experiences?*

Paper #3: Tully, L. M., Lincoln, S. H., & Hooker, C. I. (under review) Lateral prefrontal cortex dysfunction during cognitive control of emotion predicts daily social experience in schizophrenia.

Paper #3 uses functional MRI to directly test the hypothesis that schizophrenia participants have LPFC deficits during cognitive control of emotional information and that these deficits relate to daily social functioning.

Paper #1: Attentional control mediates the relationship between social anhedonia and social impairment

Submitted for publication.

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Abstract

Social anhedonia (SA), a traitlike disinterest in social contact and diminished capacity to experience pleasure from social interactions, is consistently associated with poor social functioning in both healthy and clinical populations. However, the mechanisms underlying the relationship between SA and social functioning impairments are poorly understood. Attentional control , selecting and focusing on relevant information and inhibiting the irrelevant, is impaired in high SA and is known to influence response to social stressors in healthy individuals. We examined individual differences in attentional control and its relationship to SA and social impairment in a large representative community sample of healthy adults (N=108). We hypothesized that high SA would relate to low attentional control and high social impairment. Results were consistent with hypotheses. Moreover, attentional control mediated the relationship between SA and social impairment, accounting for 19% of the variance. This has implications for our understanding of a fundamental human desire, the need to belong, and informs our understanding of the mechanisms necessary for successful social interactions.

Introduction

The desire for frequent and meaningful social interactions is a fundamental human motivation (Baumeister & Leary, 1995). Social anhedonia (SA), a trait-like disinterest in social contact and diminished capacity to experience pleasure from social interactions, is an example of when this need to belong goes awry (Silvia & Kwapil, 2011). Although socially anhedonic individuals report a genuine preference for solitude and reduced negative affect when alone (Brown, Silvia, Myin-Germeys, & Kwapil, 2007; Kwapil, et al., 2009), their asocial solitude negatively impacts their psychological well-being. High SA individuals report fewer social supports and less satisfaction with their existing social supports (Blanchard, Collins, Aghevli, Leung, & Cohen, 2011), avoidant attachment (Troisi, Alcini, Coviello, Croce Nanni, & Siracusano, 2010), decreased social competence, and overall poor social functioning (Llerena, Park, Couture, & Blanchard, 2012) - factors that are known to adversely impact important physical and mental health outcomes, possibly due to the lack of protective effects conveyed by social contact (Miller, Chen, & Cole, 2008; Silvia & Kwapil, 2011). Indeed, high SA is consistently identified as a risk factor for psychiatric disorders (Watson & Naragon-Gainey, 2010); it is one of the strongest predictive traits of conversion to schizophrenia-spectrum disorders (Kwapil, 1998), and, consistent with findings in non-clinical populations, is a key factor contributing to the characteristic social deficits in schizophrenia (Blanchard, Gangestad, Brown, & Horan, 2000; Blanchard, Mueser, & Bellack, 1998). Collectively, existing evidence consistently associates high SA with poor social functioning in both healthy and clinical populations, prompting the need for research examining the mechanisms underlying the relationship between SA and social impairments.

Although logically it follows that a reduced desire for social contact would lead to fewer friends and social engagements (i.e. poor social functioning), the underlying reason for *why* high SA individuals express reduced interest in social relationships is not entirely known. Because people with high SA also have high levels of physical anhedonia (Chapman, Chapman, & Raulin, 1976), and lower levels of positive affect (Llerena, et al., 2012), researchers have primarily focused on deficits in reward responsivity (i.e. diminished sensitivity to rewarding stimuli) as a possible cause of SA. However, another proposal is that both the causes and consequences of SA may be related to deficits in cognitive control skills, such as working memory and attentional control, which are known to be impaired in high SA and schizophrenia-spectrum populations (Nuechterlein, et al., 1998). In the context of reward processing, evidence suggests that high SA is more accurately characterized by deficits anticipating reward (i.e. anticipatory pleasure) than deficits responding to current reward (i.e. consummatory pleasure) (Gard, Kring, Gard, Horan, & Green, 2007). This indicates an impaired ability to generate representations of the reward value of future pleasurable activities (e.g. socializing with a friend), a process dependent on attentional control functions (Burbridge & Barch, 2007). This inability to create and use reward representations is thought to result in a lack of motivation to engage in pleasurable activity (Germans & Kring, 2000). Another possible consequence of attentional control deficits is the inability to control social and emotional information, particularly in social contexts, which, over-time, could significantly impair social functioning. Altogether this suggests attentional control may influence motivation for social contact and successful social functioning.

Attentional control , also termed effortful control, executive control, or cognitive control, is considered to be a self-regulatory dimension that can be operationalized as the capacity to

engage the inhibitory functions necessary to maintain task-relevant processing and goal oriented behavior (Derryberry & Reed, 2002). A core aspect of attentional control is the ability to inhibit prepotent responses in favor of subdominant ones. Socially anhedonic but otherwise healthy individuals are impaired on tasks requiring attentional control, such as the Stroop paradigm (Giraldez, Caro, Lopez Rodrigo, Paino Pineiro, & Besteiro Gonzalez, 2000) and the Wisconsin Card Sorting Task (Barrantes-Vidal, et al., 2003). However, despite this evidence demonstrating attentional control deficits in SA, the impact of these deficits on social functioning is rarely considered. Attentional control is likely a key component of successful social functioning (Heatherton & Wagner, 2011). Social interactions require the ability to filter out distracting/irrelevant information in order to attend to the relevant (e.g. in the "cocktail party" environment). This may be especially important in the context of emotional information: attentional control capabilities predict negative affect (Posner, et al., 2002), response to conflict with a partner (Hooker, et al., 2010), and response to social rejection (Gyurak, et al., 2012), indicating that deficits in the ability to use attentional control to manage social/emotional information could harm social relationships over time, thereby negatively impacting social functioning.

In our previous work, we found high SA individuals demonstrated deficits in the attentional control of emotion information on an experimental task specifically designed to assess the ability to inhibit task-incongruent irrelevant negative faces (Tully, et al., 2012). However, highly specific experimental tasks may be too narrow to capture the effect of attentional control on social functioning. Here we sought to extend these findings by examining individual differences in attentional control as it naturally varies along a continuous dimension so as to better capture the multiple inhibitory demands of the social environment.

The present study investigates the relationship between individual differences in SA, attentional control, and social impairment in a large, representative, community sample. Specifically, we investigated whether attentional control mediates the relationship between SA and social impairment. Mediation analysis provides a meaningful statistical method for describing the mechanisms through which one variable exerts an effect on another (Hayes, 2009). We assessed social anhedonia using the Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman, & Mishlove, 1982), attentional control using the Attentional Control Scale (Derryberry & Reed, 2002), and social impairment using the Social Adjustment Scale-Self-Report (Weissman, Prusoff, & Thompson, 1978). We hypothesized that: 1) High SA is associated with low attentional control and high social impairment, 2) low attentional control is associated with high social impairment, and 3) attentional control mediates the relationship between SA and social impairment.

Methods

Participants

108 participants were recruited from the Greater Boston area. Exclusion criteria: English as a second language, IQ below 70, history of head trauma, neurological or major medical illness, current/past axis I disorders, current/past personality disorders, active substance abuse within six months, current/past substance dependence. Psychopathology was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 2002) and the Structured Clinical Interview for DSM-IV Personality Disorders (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). Clinical interviews were conducted by two trained Ph.D. level clinical psychologists (LMT, SHL) and supervised by a licensed clinical psychologist (CIH). An independent clinician conducted reliability assessments on a random sample of ten

clinical interviews, revealing a kappa of 0.67, indicative of substantial diagnostic agreement (Landis & Koch, 1977).

Harvard University Institutional Review Board approved the study. Participants gave written informed consent and were paid for their participation.

Measures

Social Anhedonia. The Revised Social Anhedonia Scale (Eckblad, et al., 1982) is a 40 item true/false self-report scale measuring disinterest in social contact. Example items include: "Just being with friends can make me feel really good" (keyed false); "I attach very little importance to having close friends" (keyed true).

Attentional Control. The Attentional Control Scale (ACS; Derryberry & Reed, 2002; Fajkowska & Derryberry, 2010) is a 20 item questionnaire measuring three aspects of voluntary attention: focusing attention (9 items), shifting attention (6 items), divided attention (5 items). Example items: "I have a hard time concentrating when I'm excited about something" (focusing); "I can quickly shift from one task to another" (shifting); "My concentration is good even if there is music in the room around me" (divided). Items are rated on a 0-to-3 scale (0=never; 3=always). We used total ACS score in our primary analyses and conducted follow-up analyses using the three subscale scores.

Social Impairment. The Social Adjustment Scale–Self Report (Weissman, et al., 1978) consists of 54 questions assessing six major areas of functioning: work, social and leisure activities, relationships with extended family, role as marital partner, parental role, and role within the family unit. Areas of functioning are assessed across four categories: performance at expected tasks, level of conflict with people, interpersonal relations, and feelings and satisfactions. Area scores are averaged to create a single composite score of social impairment.

Intelligence. Full scale IQ scores were estimated using the matrix reasoning and vocabulary subtests of the Weschler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

Statistical Analysis

Data analysis was conducted with IBM SPSS 19.0. Chi square analysis and independent sample t-tests were used to assess gender differences and bivariate Pearson correlations were calculated to assess relationships between all variables. Due to 3 subjects missing data for one or more variables, the sample size used for the mediation analysis was 105.

Mediation Analysis. We assessed mediation using bootstrapping, a nonparametric resampling procedure that constructs confidence intervals for the indirect effect of the proposed mediator (Hayes, 2009). Bootstrapping has several advantages over alternative methods. Unlike traditional approaches (e.g. Sobel's z test), bootstrapping does not assume a normal distribution of the indirect effect (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002), and simulation research indicates that it has more power and better control over type I error rates compared to the causal steps approach (Baron & Kenny, 1986a) and product of coefficients approach (Sobel, 1982), particularly in small to moderate sample sizes (N<500) (MacKinnon, et al., 2002).

In a simple mediation model, where one variable (*M*) is postulated to mediate the effect of a predictor (*X*) on an outcome variable (*Y*), path coefficients are estimated using linear regression. The relationship between *X* and *Y* is termed the *total effect* (path *c*). This total effect consists of both *indirect* and *direct effects*: the indirect effect of *X* on *Y* is defined as the product of the effect of *X* on *M* (path *a*) and the effect of *M* on *Y* (path *b*), or *ab*; the direct effect of *X* on *Y* is defined as the effect of *X* on *Y* after controlling for *M* (path *c′*). Thus: $c = c' + ab$ and $ab = c - c'$ (Preacher & Hayes, 2004). Bootstrapping tests the mediation model by generating confidence intervals for the indirect effect (*ab*). The data is repeatedly resampled (with replacement),

allowing the estimation of paths *a* and *b* and the calculation of *ab*. This resampling process is repeated a total of *k* times (where *k* is some number between 1000 and 1,000,000) to build an empirical approximation of the sampling distribution of the indirect effect. Confidence intervals of the indirect effect of the mediator can then be obtained by sorting the *k* values of *ab* from smallest to largest and defining the lower and upper bounds of a confidence interval (*ci*) as the value of *ab* in the $k(.5 - ci/200)^{th}$ ordinal position (lower bound) and the $1+ k(.5 + ci/200)^{th}$ ordinal position (upper bound). If zero is not between the lower and upper bounds of the confidence interval, it can be inferred that the indirect effect is significantly different from zero, indicating that the mediating variable accounts for some portion of the relationship between *X* and *Y* (Hayes, 2009). The portion of variance uniquely associated with the mediated effect (R^2_{med}) can then be calculated on the basis of partial correlations, providing information regarding the magnitude of the effect of *X* on *Y* through *M* (Fairchild, MacKinnon, Taborga, & Taylor, 2009).

Mediation analysis for a multiple mediator model, where two or more variables (M_j) are postulated to mediate the effect of predictor *X* on outcome variable *Y*, is a straightforward extension of the single mediator model. As in the single mediator model, path *c* represents the *total effect* of *X* on *Y* and path *c'* represents the *direct effect* of X on Y after adjusting for the mediators. The products of paths a_j and b_j (i.e. a_1b_1, a_2b_2, a_3b_3) represent the mediated effects in the model, termed *specific indirect effects* (Bollen, 1987). Bootstrapping methods can then be used to test each mediator by generating confidence intervals for each specific indirect effect. Pairwise contrasts can be used to examine the relative magnitude of the specific indirect effects. These are obtained by calculating the difference, dividing by its standard error, and deriving a *p* value from the standard normal distribution.

Here we assessed two mediation models: a single mediator model testing the effect of SA on social impairment through overall self-reported attentional control, followed by a multiple mediator model to determine the specific indirect effects of the three aspects of attentional control (focusing, divided, and shifting attention) on the relationship between SA and social impairment. We conducted bootstrap analysis with the SPSS macro INDIRECT from Preacher and Hayes (2008) to obtain estimates of the indirect effects and associated 95% confidence intervals using the recommended 5000 bootstrap samples. We used the SPSS macro RSQUARE from Fairchild et al.(2009) to calculate the portion of variance accounted for by the mediated effect of AC (R^2_{med}).

Table 1. Demographics and Sample Characteristics

	Total Sample	Male	Female	Gender Differences
N	108	50	58	χ^2 (1) = 0.539, p = 0.441
Age	30.95 (12.87), [18-65]	32.32 (13.07), [18-64]	29.78 (12.69), [18-65]	t(106) = 1.024, p = 0.308
WASI IQ [a]	112.64 (12.92), [81-137]	112.63 (13.52), [81-137]	112.64 (12.51), [82-136]	t(105) = 0.002, p = 0.998
Social Anhedonia	12.71 (11.08), [0-40]	13.88 (11.22), [0-38]	11.71 (10.96), [0-40]	t(106) = 1.016, p = 0.312
Attentional Control	55.31 (12.61), [7-78]	56.94 (11.88), [25-78]	53.91 (13.15), [7-74]	t(106) = 1.246, p = 0.215
Social Impairment [b]	58.85 (15.11), [36-109]	61.38 (16.90), [36-109]	56.72 (13.20), [36-89]	t(103) = 1.158, p = 0.116

Note: All data are presented as: mean (SD), [range]
[a] one participant did not complete the WASI IQ
[b] one participant did not complete the SAS-SR

Results

Table 1 presents demographics and sample characteristics. There were no gender differences on any demographic or self-report measures. Table 2 presents bivariate Pearson correlation coefficients between IQ and all self-report variables. SA, attentional control, and social impairment were all significantly intercorrelated in the predicted directions; higher SA related to lower attentional control and greater social impairments, and lower attentional control related to higher social impairment. IQ did not significantly relate to any variables, indicating that these relationships are not due to IQ.

Table 2. Correlations between all variables

	1	2	3	4
1. IQ	-			
2. Social Anhedonia	-0.11	-		
3. Attentional Control	0.05	-0.42**	-	
4. Social Impairment	-0.07	0.66**	-0.49**	-

**p<0.001

Mediation Analysis. We assessed the single mediator model in which attentional control is hypothesized to mediate the relationship between social anhedonia and social impairment. All four paths were significant in the predicted directions (Figure 1A): SA had a total positive effect on social impairment (β=0.89, p<0.001), and a total negative effect on attentional control (β=-0.47, p<0.001); attentional control had a direct negative effect on social impairment (β=-0.31, p=0.001). Bootstrap analysis of the indirect effect (Table 3) revealed a bias corrected 95% confidence interval excluding zero (CI_{95}=0.06, 0.28), demonstrating that attentional control mediates the relationship between SA and social impairment. The direct effect of SA on social impairment, controlling for attentional control, remained significant (β=0.75, p<0.001),

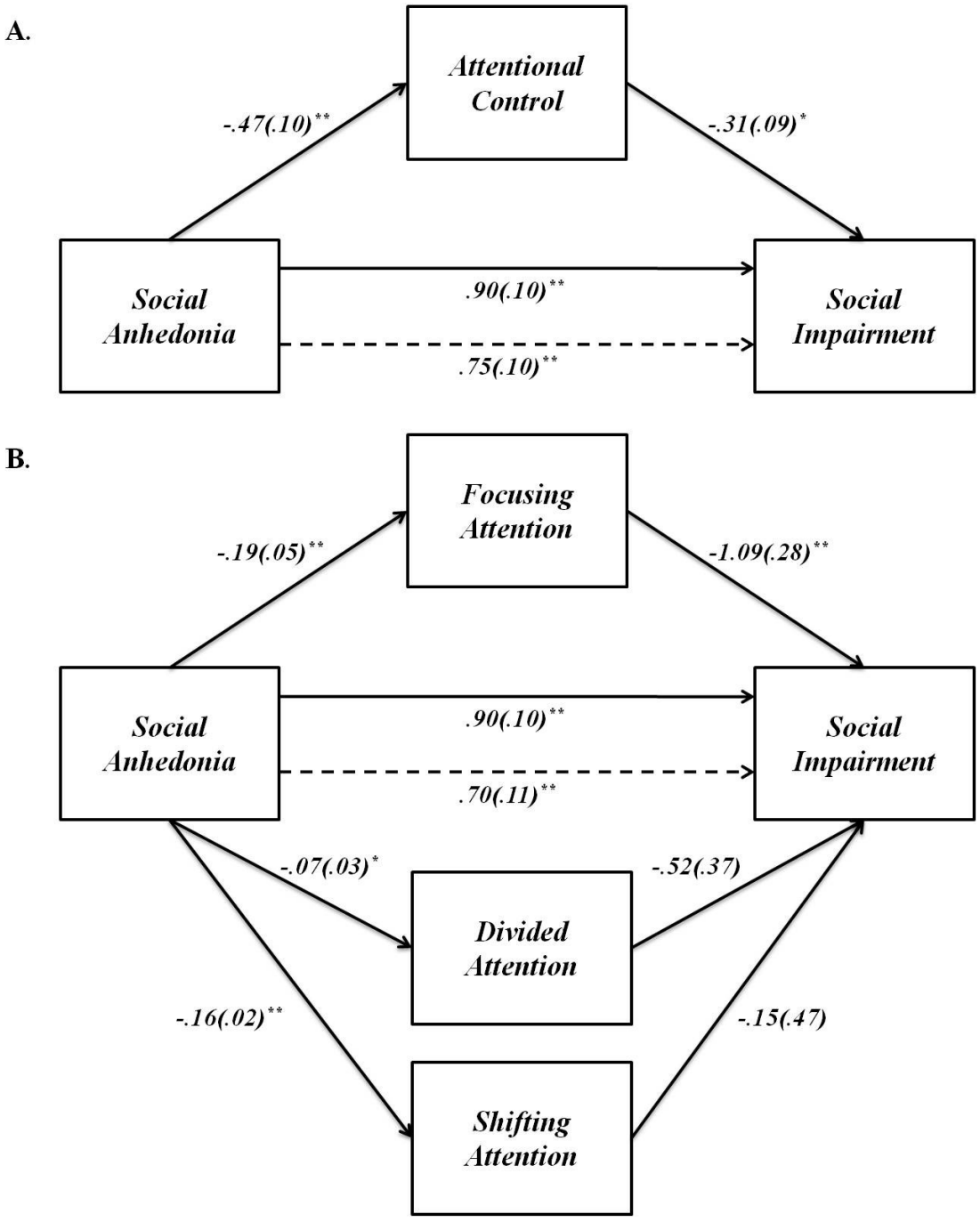

Figure 1. (A) The effect of SA on social impairment through attentional control. (B) The effect of SA on social impairment through the three components of attentional control: focusing, divided, and shifting attention. Unstandardized path coefficients (SE) shown for each path.**p<0.001;*p<0.05

Table 3. Mediation of the effect of social anhedonia on social impairment through attentional control

					BC 95% CI	
Indirect Effect	**Coefficient**	**Point Estimate**	**Bias**	**SE**	**Lower**	**Upper**
SA on social impairment through attentional control	0.147	0.151	0.005	0.057	0.063	0.289

Table 4. Mediation of the effect of social anhedonia on social impairment through the three specific components of attentional control: focusing attention, divided attention, and shifting attention

					BC 95% CI	
Specific Indirect Effect	**Coefficient**	**Point Estimate**	**Bias**	**SE**	**Lower**	**Upper**
Indirect Effects						
Focusing	0.204	0.202	-0.002	0.069	0.089	0.360
Divided	-0.034	-0.035	-0.001	0.033	-0.127	0.006
Shifting	0.025	0.032	0.007	0.080	-0.124	0.195
TOTAL	0.195	0.198	0.003	0.079	0.057	0.373
Contrasts						
Focusing vs. divided	0.238	0.238	-0.001	0.089	0.099	0.455
Focusing vs. shifting	0.179	0.171	-0.009	0.116	-0.046	0.415
Divided vs. shifting	-0.059	-0.067	-0.008	0.094	-0.270	0.108

Note: Coefficients are unstandardized; Bias = difference between indirect effect in original sample and bootstrap derived point estimate; SE = bootstrap derived estimate of standard error of indirect effect; BC = bias corrected; CI = confidence interval; 5000 bootstrap samples

indicating that attentional control only partially mediates the relationship between SA and social impairment. The mediated effect of SA on social impairment through attentional control accounts for 19% of the variance in social impairment (R^2_{med}=0.19, $CI_{.95}$=0.08, 0.32).

We examined the specific indirect effects of the three components of attentional control in a multiple mediator model (Figure 1B). SA had negative effects on all three components of attentional control: focusing (β=-0.19, p<0.001), divided (β=-0.07, p<0.05), and shifting attention (β=-0.16, p<0.001). However, only focusing attention had a significant indirect effect on social impairment (β=-1.09, p<0.001); all other paths between components of attentional control and social impairment were non-significant (all p>0.1). Bootstrap analysis (Table 4) of the specific indirect effect of focusing attention on the relationship between social anhedonia and social impairment revealed a bias corrected 95% confidence interval excluding zero ($CI_{.95}$=0.09, 0.36). Confidence intervals for the specific indirect effects of divided attention and shifting attention both included zero, indicating that the relationship between social anhedonia and social impairment is partially mediated by one specific aspect of attentional control – focusing attention. Pairwise contrasts revealed the specific indirect effect through focusing attention is larger in magnitude than the specific indirect effect through divided attention. All other pairwise contrasts were non-significant (Table 4).

Collectively, these results indicate that attentional control, specifically focusing attention, is a contributing mechanism underlying the relationship between SA and social impairment.

Discussion

This study examined the relationship between individual differences in social anhedonia, attentional control, and social impairment in a large community sample of healthy individuals. Two main findings emerged: first, we replicated the association between high SA and high social

impairment found in previous studies (Blanchard, et al., 2011; Cohen, Leung, Saperstein, & Blanchard, 2006; Katsanis, Iacono, Beiser, & Lacey, 1992) providing further evidence for the presence of social impairments in socially anhedonic but otherwise healthy individuals. Second, attentional control partially mediated the relationship between SA and social impairment, accounting for 19% of the variance. Specifically, individuals with higher SA reported lower attentional control and lower social functioning. Although both attentional deficits and social impairments have been separately noted in SA, the relationship between SA, attentional control and social impairments in this large non-clinical sample is a novel contribution to the literature. These findings establish attentional control as one of the mechanisms underlying aberrations in the fundamental human need for social contact, indicating that the ability to engage attentional control processes, specifically focusing attention in the presence of irrelevant and distracting stimuli, is a cognitive feature of social anhedonia that contributes to social impairments.

Our results also have implications for understanding how a core negative symptom of schizophrenia relates to the characteristic social impairments of the illness. Furthermore, our findings are consistent with evidence demonstrating attentional control deficits in high SA and schizophrenia samples, providing further support for the proposal that impaired attentional processes are characteristic of schizophrenia liability (Erlenmeyer-Kimling & Cornblatt, 1992).

Our findings demonstrate attentional control is a proximal mediator, meaning that it is more closely related to SA than social impairment (Hoyle & Kenny, 1999). This suggests that the effect of attentional control on social functioning may operate through additional variables that reflect the multiple ways that attentional control is used in social contexts. For example, one proposed route is through the role of attentional control in the regulation of affective information. Social interactions by nature involve affectively salient information, thus deficits in

the regulation of affective information could adversely affect response to interpersonal stressors and consequently social functioning. Our prior research is consistent with this proposal. Impaired attentional control in schizophrenia contributes to negative affective information exerting inappropriate influence on social judgments (Hooker, et al., 2011), and failure to recruit neural mechanisms of attentional control predicts maladaptive responses to interpersonal conflict in healthy (Hooker, et al., 2010), schizophrenia (Tully, Lincoln, & Hooker, under review), and high SA samples (Hooker, et al., under review). Additionally, impaired engagement of attentional control mechanisms to down-regulate negative affective information could be accompanied by a complimentary deficit in the up-regulation of positive affective information, which is thought to underlie the anticipatory pleasure deficit in anhedonia (Pizzagalli, 2010) and could contribute to the associated reward/motivational impairments seen in high SA (Horan, Blanchard, Clark, & Green, 2008). Preliminary evidence is consistent with this proposed role for attentional control in the management of both positive and negative affect (e.g. Vasey, Harbaugh, Mikolich, Firestone, & Bijttebier, 2013), but the connection to SA and social functioning has yet to be made. Future research should test this possibility by including measures of attentional control of affective information, both positive and negative, to identify additional and related mediators of the relationship between SA and social functioning.

It is important to note that the current study is unable to establish causal directions between variables because of its cross-sectional design; a statistically significant mediated effect does not determine the causal direction of a relationship (Preacher & Hayes, 2004). We conducted the current study on a theoretical foundation based on prior research demonstrating that SA predicts social impairment (Blanchard, et al., 2011; Cohen, et al., 2006; Katsanis, et al., 1992) and that SA can be partially characterized by attentional control deficits (Barrantes-Vidal,

et al., 2003; Giraldez, et al., 2000), leading us to hypothesize that attentional control is an underlying characteristic of high SA that explains the relationship between SA and social impairment. However, only a longitudinal study design in which attentional control and social anhedonia are tracked across the life span in relation to social functioning can truly determine causal priority of the model. The New York High Risk Project partially investigated this in relation to *physical* anhedonia and attention in a longitudinal follow-up of individuals at genetic risk for schizophrenia (Erlenmeyer-Kimling, et al., 1993). Results indicated that poor attentional capabilities as a child predicted physical anhedonia as an adolescent, which in turn predicted social functioning as an adult. It is possible that a similar causal relationship in which low attentional control causes high SA and consequently high social impairment; future research should conduct longitudinal examination of this causal pathway.

Conclusion

The current study demonstrates that the relationship between social anhedonia and social impairment is partially mediated by attentional control. This has implications for our understanding of a fundamental human desire, the need to belong, and informs our understanding of the mechanisms necessary for successful social interactions. This finding also illuminates one of the mechanisms underlying the relationship between a well-established negative symptom of schizophrenia and social impairment, and suggests that improving attentional control skills could reduce social impairment in populations at risk for schizophrenia.

Paper #2: Impaired cognitive control mediates the relationship between abnormalities in cortical thickness of the superior frontal gyrus and role functioning in schizophrenia

In preparation for publication.

Authors

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Abstract

The neuroanatomical basis of functional impairment in schizophrenia is poorly understood. Structural abnormalities in the lateral prefrontal cortex are well-documented in schizophrenia, and more recent evidence suggests a relationship between these abnormalities and functioning. Cognitive control mechanisms, reliant on the lateral prefrontal cortex, are impaired in schizophrenia and predict functional outcome. This study used surface-based morphometry to investigate relationships between cortical surface characteristics, cognitive control, and measures of social and role functioning in a sample of individuals with schizophrenia and a group of demographically-matched healthy controls. Results demonstrated that compared to healthy controls, schizophrenia participants had thinner cortex in a region of the superior frontal gyrus (BA10). Across all participants, decreased cortical thickness in this region related to decreased cognitive control and decreased role functioning. Moreover, cognitive control fully mediated the relationship between cortical thickness in the SFG and role functioning, indicating that neuroanatomical abnormalities in the SFG adversely impacts role functioning via impaired cognitive control processes.

Introduction

Deficits in social and role functioning (i.e. work/school outcomes) are among the most pervasive and disabling of impairments in schizophrenia (APA, 2000; Couture, et al., 2006). Effective management of the complex demands of daily life requires the engagement of top-down inhibitory and facilitatory processes necessary to maintain task-relevant processing and coordinate appropriate behavioral responses. As such, impairments in these self-regulatory processes, involving cognitive control mechanisms reliant on a fronto-parietal network (Bush & Shin, 2006; Lesh, et al., 2011), may contribute to poor social and role functioning (Heatherton & Wagner, 2011). Both functional and morphological abnormalities in the cognitive control network are well established in schizophrenia, particularly in lateral prefrontal cortex (Barch, 2005; Shenton, Dickey, Frumin, & McCarley, 2001), such that lateral prefrontal dysfunction has been proposed as a biomarker for the illness (Lesh, et al., 2011; Woodward, et al., 2009). However, the relationship between neural abnormalities in the lateral prefrontal regions and functional impairment has received limited attention in the literature, thus how they impact functioning remains unknown. One proposal is that neural abnormalities in lateral prefrontal cortices reflect a neurobiological vulnerability that affects functioning via impaired cognitive control. The present study tests this proposal by examining the link between lateral prefrontal morphology, cognitive control and functioning in schizophrenia.

Functional neuroimaging studies indicate a fronto-parietal network of cognitive control, in which the lateral prefrontal cortex (LPFC) exerts top-down regulation of task-oriented processing (Bush, Luu, & Posner, 2000; Bush & Shin, 2006; Duncan & Owen, 2000). Individuals with schizophrenia have consistently show abnormal activation in the LPFC during cognitive control tasks (Minzenberg, et al., 2009), paralleling well-documented impairments on

behavioral measures (Heinrichs & Zakzanis, 1998). Damage to these brain regions is associated with similar deficits in response inhibition and cognitive control (Burgess, et al., 2000; Miller, 2000), suggesting that the observed neurofunctional abnormalities in the cognitive control network in schizophrenia may be rooted in neuroanatomical abnormalities. Consistent with this proposal, structural neuroimaging studies routinely demonstrate abnormalities in the LPFC (e.g. Honea, et al., 2005; Janssen, et al., 2009; Kuperberg, et al., 2003; Shenton, et al., 2001; Venkatasubramanian, et al., 2008; Wisco, et al., 2007). Moreover, recent findings show a pattern of reduced cortical thickness/grey matter volume in lateral prefrontal regions relating to increased symptoms (Zierhut, et al., in press) and decreased global functioning (Chemerinski, et al., 2002; Kasparek, et al., 2009; Prasad, et al., 2005), indicating a relationship between LPFC morphology and core clinical characteristics of schizophrenia. Given the role of LPFC regions in cognitive control, it is possible that impaired cognitive control mediates this relationship.

Several studies have demonstrated a relationship between LPFC structure and performance on behavioral tasks assessing executive functioning and cognitive control in schizophrenia. Reduced grey matter volume (GMV) relates to poor performance on tasks, including the Wisconsin Card Sorting Task (WCST; Ho, et al., 2003; Seidman, et al., 1994), the continuous performance task (Salgado-Pineda, et al., 2004), the N-back (Zierhut, et al., in press) and the Controlled Oral Word Association Test (COWAT; Minatogawa-Chang, et al., 2009) - all tasks that involve the core aspect of cognitive control (i.e. the ability inhibit prepotent responses in favor of subdominant ones), and are known to predict functional outcome (Addington & Addington, 2000; Green, 1998; Milev, et al., 2005). Collectively, these data suggest that structural abnormalities in the LPFC affect functioning through cognitive control processes.

However, to our knowledge no studies have examined the putative indirect effect of neuroanatomical abnormalities on functional impairments through cognitive control.

This study had two aims: first, we sought to compare cortical thickness and surface area between groups, with particular interest in hypothesized group differences in cognitive control related region, the lateral prefrontal cortex. Second, we sought to examine the relationship between identified group differences in cortical thickness and/or surface area to behavioral measures of cognitive control and functioning. Specifically, we investigated whether cognitive control mediates the relationship between disease-related variations in lateral prefrontal cortical thickness/surface area and measures of functioning. We used surface-based morphometry (SBM) methods to investigate neuroanatomical characteristics of the cortical surface in a sample of schizophrenia and healthy control participants. SBM offers the ability to examine cortical thickness and surface area independently, which despite sharing high heritability, are believed to be determined by separate genetic mechanisms (Panizzon, et al., 2009; Winkler, et al., 2010). Therefore examining them separately in relation to putative cognitive endophenotypes may be a more sensitive measure of neurobiological substrates of functional impairments in schizophrenia than the more commonly used measure of gray matter volume (GMV). Moreover, since cortical volume is derived from both thickness and surface area, the averaging of these two features could obscure pathophysiological characteristics present independently in each feature (Fornito, et al., 2008), and their relationship to functioning measures. Here we use Freesurfer, an SBM analysis suite (http://surfer.nmr.mgh.harvard.edu), that measures cortical thickness within an accuracy of .2mm (Rosas, et al., 2002) and has been well validated across MRI protocols (Fischl & Dale, 2000).

For our measures of cognitive control we chose the Continuous Performance Test - Identical Pairs (CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988), and the category fluency animal naming test (Spreen & Strauss, 1991). Although the CPT-IP is typically classified as a measure of sustained attention, optimal performance requires engagement of cognitive control processes for the inhibition of commission errors to false trials, and the primary outcome measure of the task, the ratio between correct responses and commission errors, can be interpreted as a measure of cognitive control. Similarly, although primarily classified as a verbal fluency task testing semantic processing, the category fluency task has long been considered an index of frontal lobe executive functioning (Baddeley, Della Sala, Papagno, & Spinnler, 1997) given the task's demands for a directed, cognitive control dependent search for words, facilitation of efficient set switching between sub-categories of words (e.g. from farm animals to jungle animals), and inhibition of non-category items (Rende, Ramsberger, & Miyake, 2002). Poor performance on both the CPT and category fluency tasks have been associated with abnormal neural function (Azechi, et al., 2010; Kubota, et al., 2005; Riccio, Reynolds, Lowe, & Moore, 2002) and structure (Minatogawa-Chang, et al., 2009; Salgado-Pineda, et al., 2004) in lateral prefrontal regions in schizophrenia, indicating that both tasks are sensitive assessments of LPFC mediated cognitive control processes. Finally, for our measures of functioning we used the Global Functioning Social (GFS; Auther, Smith, & Cornblatt, 2006) and Role (GFR; Niendam, Bearden, Johnson, & Cannon, 2006) scales so as to delineate between functioning in interpersonal and work/school settings.

We hypothesized: 1) Compared to healthy participants, schizophrenia participants will have reduced cortical thickness and surface area in the lateral prefrontal cortex.; 2) Reduced cortical thickness and/or surface area in regions with identified group differences will relate to

decreased performance on behavioral measures of cognitive control and decreased functioning; 3) cognitive control will mediate the relationship between cortical thickness/surface area and functioning.

Methods

Participants

26 individuals with schizophrenia or schizoaffective disorder and 29 healthy controls matched for age, gender, years of education and IQ were recruited from the Greater Boston area (Table 5). Inclusion criteria for all participants: age 18-65, IQ above 70, primary English speaker, no history of head trauma, neurological or major medical illness, no substance abuse within six months, no current/past substance dependence. Inclusion criteria for schizophrenia participants: diagnosis of schizophrenia or schizoaffective disorder, no co-morbid axis I disorders, no history of electroconvulsive therapy. Inclusion criteria for healthy participants: no current/past axis I disorders, no first-degree relative with a psychotic disorder, and scores within 1.5 standard deviations of the population mean on five measures schizotypal personality: the perceptual aberration scale (Chapman, et al., 1976), magical ideation scale (Eckblad & Chapman, 1983), referential thinking scale (Lenzenweger, Bennett, & Lilenfeld, 1997), physical anhedonia scale (Chapman, et al., 1976), revised social anhedonia scale (Eckblad, et al., 1982). Full scale IQ was estimated using the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Psychopathology was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First, et al., 2002). Clinical assessments were conducted by trained PhD-level clinical psychologists (LMT, SHL) supervised by a licensed clinical psychologist (CIH). Harvard University Institutional Review Board approved the study.

Table 5. Demographics and behavioral data

	SZ Group	Control Group	Differences Between Groups
N	26	29	
Gender (M/F)	16/10	20/9	$X^2(1) = 0.33$, $p = 0.56$
Age	38.69 (10.28) [21-58]	33.76 (12.38) [18-55]	$t(53) = 1.60$, $p = 0.12$
Education	14.69 (2.15) [10-18]	14.59 (2.64) [11-21]	$t(53) = 0.16$, $p = 0.87$
IQ [a]	108.08 (13.32) [82-133]	110.69 (11.60) [87-130]	$t(53) = 0.78$, $p = 0.44$
Diagnosis [b]			
Schizophrenia N (%)	20 (77%)		
Schizoaffective N (%)	6 (23%)		
Age of Illness Onset	22.24 (4.94) [13-34]		
Length of Illness	16.40 (12.02) [1-42]		
Antipsychotic Medication [c]			
Atypical N (%)	19 (73%)		
Typical N (%)	3 (12%)		
None N (%)	3 (12%)		
CPZ Equivalent [d]	461.11 (416.91) [0-1600]		
Cognitive Control			
CPT-IP	2.59 (0.66) [1-4]	3.05 (0.64) [1-4]	$t(53) = 2.61$, $p = 0.01$, $d = 0.72$[e]
Category Fluency	47.08 (9.21) [32-66]	55.00 (8.61) [39-74]	$t(53) = 3.30$, $p < 0.01$, $d = 0.91$
Functioning			
Social Functioning	6.08 (1.79) [3-9]	8.66 (1.26) [6-10]	$t(53) = 6.23$, $p < 0.001$, $d = 1.71$
Role Functioning	5.31 (1.89) [2-8]	8.38 (1.18) [6-10]	$t(53) = 7.31$, $p < 0.001$, $d = 2.01$

Note: data represent mean (SD) [range] unless otherwise indicated. [a] Full scale IQ scores were estimated using the vocabulary and matrix reasoning subtests of the Weschler Abbreviated Scale of Intelligence (WASI); [b] Subtypes of the 20 participants with schizophrenia were: 16 Paranoid, 3 Residual, and 1 Undifferentiated. Subtypes of the 6 participants with Schizoaffective disorder were: 3 Bipolar, and 3 Depressive; [c] One patient did not report medication; [d] CPZ = Chlopromazine equivalents calculated using methods described in Woods (2003) [e] Cohen's d effect size.

Participants gave written informed consent and were paid for their participation.

Assessments

Cognitive control. We assessed cognitive control using the Continuous Performance Task - Identical Pairs (Cornblatt, et al., 1988), and the category fluency animal naming task (Spreen & Strauss, 1991).

In the CPT-IP participants are presented with a series of 2-digit, 3-digit, and 4-digit numbers in rapid succession and must respond when the same number appears twice in sequence. In order to minimize commission errors (false alarms) to numbers that are similar but not identical (e.g. 2256 followed by 2265) participants must engage inhibitory mechanisms of cognitive control processes and continue to direct attention to the task-demand of correctly identifying sequential presentation of identical numbers. Therefore the primary outcome variable - d' (the ratio of correct hits to false alarms) - can be interpreted as a measure of cognitive control; higher d' values reflect better cognitive control.

In the category fluency task participants have 60 seconds to generate as many animal names as they can. Although typically classified as a verbal fluency task testing semantic processing, optimal task performance also requires intact lateral prefrontal mediated cognitive control processes to direct and maintain semantic activation in a task appropriate context (Rende, et al., 2002). Therefore the outcome measure - the total number of animals named - can be interpreted as a measure of cognitive control processes; higher scores reflect better cognitive control.

Social and Role Functioning Clinician rated social and role functioning was obtained using the Global Functioning: Social Scale (GFS; Auther, et al., 2006) and Global Functioning: Role Scale (GFR; Niendam, et al., 2006). The GFR and GFS provide single overall scores

broadly based on the format of the Global Assessment of Functioning Scale (GAF; APA, 2000) but with the stipulation that ratings are made regardless of aetiology or symptomatology so as to avoid confounding functioning and psychiatric symptoms (Cornblatt, et al., 2007). Scores range from 1 to 10 on both scales. Higher scores indicate better functioning such that a 10 represents superior functioning and a 1 represents extreme dysfunction. The GFS assesses four main areas of social functioning: involvement with family members, age appropriate intimate relationships, quantity and quality of peer relationships, and level of peer conflict. The GFR assesses functioning in school, work, or as a homemaker, depending on age and the primary role of the individual. Ratings are made based on age appropriateness, demands of the role, level of independence, and overall performance in the role.

Magnetic resonance imaging

Image acquisition. High resolution anatomical brain images were acquired on a Siemens 3T Tim Trio scanner (Siemens Sonata, Erlangen, Germany) with a 32 channel whole-head coil using a 3-dimensional T1-weighted multi-echo magnetization-prepared rapid acquisition of gradient-echo (MEMPRAGE) sequence (176 contiguous 1mm anterior commissure - posterior commissure slices; acceleration factor of 2; voxel size, 1mm x 1mm x 1mm; flip angle, 7 degrees; TR, 2530 ms; TE, 7.22 ms; FOV, 256mm x 256mm; matrix size, 256 x 256; total acquisition time = 6 minutes, 44 seconds). Head movement was minimized using foam padding in the head coil and subjects wore earplugs to muffle scanner noise.

Image Processing and calculation of cortical thickness and surface area. Images were processed with Freesurfer image analysis suite (version 5.1.0), using procedures detailed in prior publications (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Briefly, images are transformed using an affine registration to Montreal Neurological Institute space (MNI),

intensity normalized, skull-stripped, and segmented into grey and white matter tissues based on voxel location and intensity and the intensities of neighboring voxels. Cutting planes based on the location of the corpus callosum and pons in MNI space are computed to separate the cerebral hemispheres, remove the cerebellum and brain stem, and disconnect subcortical and cortical components. Any interior holes in the white matter components are filled, creating a single filled white matter volume for each hemisphere. The white matter surface is reconstructed by building a mesh of triangular faces on the outside of the white matter mass, using two triangles per exposed voxel face. Each triangle is termed a vertex and is the surface-based analog of a voxel. The tessellated white matter surface is then refined by adjusting for intensity gradients between white and grey matter, smoothed, and topological defects are automatically corrected (Dale & Sereno, 1993; Fischl, Liu, & Dale, 2001). This surface is referred to as the *white surface.* The *pial surface* (i.e. grey matter/cerebrospinal fluid boundary) is then produced by outward deformation of the white surface (i.e. nudging the white boundary outwards) until the tissue contrast is maximal (Fischl & Dale, 2000). The surfaces are then spherically inflated for surface-based intersubject registration to a spherical atlas based on folding patterns - directly aligning surfaces based on shared cortical anatomy rather than image intensities, thereby minimizing metric distortion and creating vertex-to-vertex correspondence across subjects (Fischl, Sereno, Tootell, & Dale, 1999). Finally, neuroanatomical labels are assigned to each vertex via an automatic parcellation algorithm that combines probabilistic information from the cortical model with neuroanatomical convention from a manually labeled training data set (Fischl, et al., 2002). We used the regions of the Destrieux atlas because of its more functionally informed parcellation of the lateral prefrontal cortices (Fischl, et al., 2004). Using information from the white and pial surfaces, measures of cortical thickness and surface area are calculated at each vertex. Cortical

thickness is calculated by finding the shortest distance between a given point on the white surface to the pial surface and vice versa and averaging the two values; cortical surface area is calculated as the average of the area of triangle-faces that touch each vertex.

Statistical analysis

All variables were screened for normalcy and outliers. Two variables identified as significantly skewed (role functioning and mean cortical thickness in the superior frontal gyrus) were log transformed. Two participants in the healthy control group did not complete the CPT-IP or the category fluency task, and one participant in the schizophrenia group did not complete the CPT-IP; missing scores were replaced with the mean of the given group.

Demographic and behavioral Data. Analysis of behavioral data was conducted in IBM SPSS v. 20.0. We used chi-square and independent t-tests to assess group differences on demographic and behavioral variables, and Pearson correlations to assess relationships between measures of cognitive control and functioning.

Analysis of cortical thickness and surface area. Cortical thickness and surface area statistical maps were created by mapping each subject's surface data to a common spherical coordinate system and smoothed using a 10mm full-width-half-maximum gaussian filter. To examine group differences in cortical parameters we conducted general linear models (GLMs) comparing cortical parameter maps (thickness/surface area) between healthy and schizophrenia individuals at every vertex over the whole cortex for each hemisphere (i.e. whole cortex vertex-by-vertex analysis). For all analyses left and right hemispheres were tested separately.

Correction for multiple comparisons and cluster identification. We corrected for multiple comparisons using Monte-Carlo permutation cluster analyses conducted in Freesurfer (Hagler et al. 2006) with a vertex threshold of $p<0.05$ (two-tailed) and a cluster-wise threshold

(p_{cw}) of p_{cw}<0.025 (i,e. p_{cw}< 0.05 Bonferroni corrected across two hemispheres). This statistical approach and has been used in prior publications using SBM methods in schizophrenia samples (e.g. Wisco, et al., 2007). Statistics for identified clusters, including cluster size (mm^2) and number of vertices, MNI coordinates, and p_{cw} are reported.

Confounds: Age, gender, and mean cortical parameters. To account for confounding effects of variables known to influence SBM the following covariates were entered into all models: age, gender, and mean cortical parameter for the given hemisphere in the given analysis (i.e. mean cortical thickness for the whole left hemisphere was entered into models testing group/variable related effects on cortical thickness in the left hemisphere; idem for surface area analyses).

Analyses related to each specific hypothesis are reported below.

Hypothesis 1: Compared to healthy participants, schizophrenia participants will have reduced cortical thickness and/or surface area in the lateral prefrontal cortex.

We assessed group differences in cortical thickness and surface area using two GLMs (one for each hemisphere) modeling the given cortical parameter (thickness/area) as a function of group at each vertex in the whole brain. The mean cortical parameter was extracted from any clusters that survived correction for multiple comparisons and used in follow up analyses in SPSS to test our second and third hypotheses (see below).

Hypothesis 2: Reduced cortical thickness and/or surface area in regions with identified group differences will relate to decreased performance on behavioral measures of cognitive control and decreased functioning.

Data from SBM analysis was used to test the hypothesis that abnormalities in schizophrenia participants' cortical sheet would related to decreased cognitive control and

decreased functioning. Cortical abnormalities were identified as regions where schizophrenia participants had reduced cortical thickness/surface area compared to healthy controls. Results from the SBM analysis of cortical thickness revealed a 784.18mm^2 cluster with peak MNI coordinates (x =-10.4, y= 60.9, z=19.6) in the superior frontal gyrus (SFG) BA 10. Mean cortical thickness values for each subject in this cluster were extracted and bivariate Pearson correlations were conducted between these mean cortical thickness values and behavioral measures of cognitive control and functioning.

Hypothesis 3: Cognitive control will mediate the relationship between cortical thickness/surface area and functioning.

Data from correlational analysis revealed significant intercorrelations between cortical thickness in the SFG, cognitive control, and role functioning. Thus to test our third hypothesis that the relationship between cortical thickness in the LPFC and functioning is mediated by cognitive control, we entered SFG cortical thickness, cognitive control, and role functioning into a single mediation model. We assessed mediation using bootstrapping across all participants. Bootstrapping is a nonparametric resampling procedure that constructs confidence intervals for the indirect effect of the proposed mediator (Hayes, 2009), that has more power to detect mediated effects in small samples (MacKinnon, et al., 2002) compared to the causal steps approach (Baron & Kenny, 1986b) and product of coefficients approach (Sobel, 1982). We conducted bootstrapping analysis with the SPSS macro PROCESS from Hayes (2013) to obtain estimates of the total, direct, and indirect effects and associated 95% confidence intervals using the recommended 5000 bootstrap samples. PROCESS also produces two measures of effect size that are useful: R^2_{med}, which accounts for the portion of variance in the outcome variable that the predictor and mediator share, and κ^2 ("kappa squared") which expresses the size of the indirect

effect in terms of a ratio to the maximum possible indirect effect that could have been found. For κ^2 a small effect is 0.01, a medium effect is 0.09, and a large effect is 0.25 or above (Preacher & Kelley, 2011).

Results

Demographic and behavioral data

There were no group differences in age, gender, IQ, or years of education (Table 5). Consistent with prior literature, schizophrenia participants performed significantly worse than healthy individuals on both the CPT-IP ($t(53)=2.61$, $p=0.012$) and category fluency ($t(53)=3.30$, $p=0.002$), indicating impaired cognitive control capabilities. Schizophrenia participants also demonstrated expected deficits in social ($t(53)=7.31$, $p<0.001$) and role ($t(53)=6.23$, $p<0.001$) functioning.

Analysis of cortical thickness and surface area

Hypothesis 1: Schizophrenia participants have abnormalities in cortical thickness and cortical surface area.

Cortical thickness. Whole-brain analysis identified one cluster where schizophrenia participants showed thinner cortex compared to healthy controls in the left superior frontal/middle frontal gyral region of BA10 (MNI: x =-10.4, y= 60.9, z=19.6; $p_{cw}=0.017$; surface area=811.78mm^2) (Figure 2). No clusters showing group differences were detected in the right hemisphere. There were no clusters detected in either hemisphere where schizophrenia participants had increased thickness compared to healthy individuals.

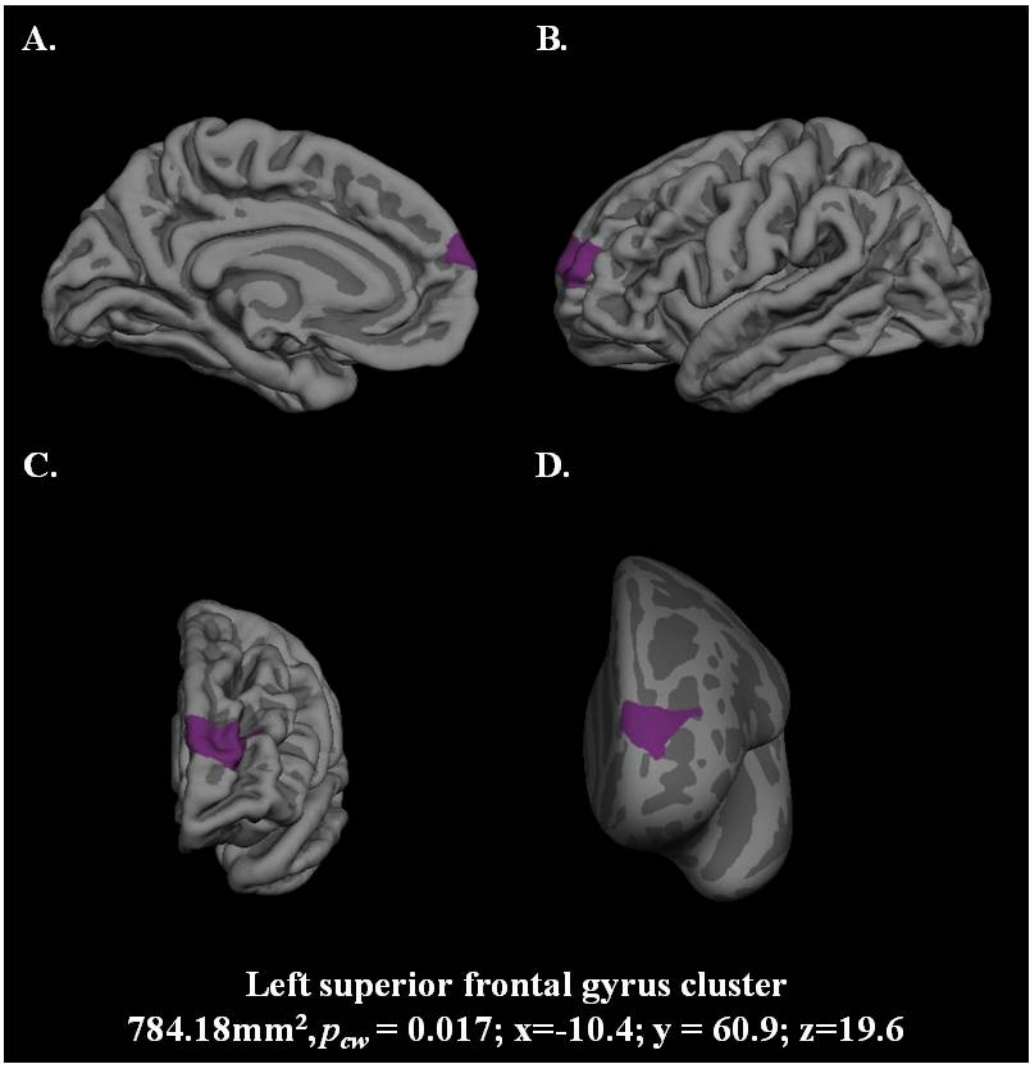

Figure 2. Left hemisphere views of group differences in cortical thickness presented on average cortical surface template overlayed with curvature map (light grey regions are gyri; dark grey regions are sulci). A, medial; B, lateral; C, anterior, and D, anterior inflated. Purple region represents cluster identified in the superior frontal gyrus (BA10) where schizophrenia participants (n=26) had thinner cortex compared to healthy controls (n=29). Cluster size = 784.18mm^2; clusterwise p-value = 0.017; MNI coordinates of peak F-ratio value: x = -10.4; y = 60.9; z = 19.6. Statistical analysis was performed fitting a general linear model at every vertex, with age, gender, and mean cortical thickness of the left hemisphere as covariates. Correction for multiple comparisons was done with Monte Carlo permutation analyses (see methods).

Cortical surface area. No clusters showing significant group differences in cortical surface area were identified in either direction, in either hemisphere.

Hypothesis 2: Reduced cortical thickness in regions with identified group differences will relate to decreased performance on behavioral measures of cognitive control and decreased functioning.

To test our second hypothesis we extracted mean cortical thickness data from the cluster in the superior frontal gyrus (SFG) where schizophrenia patients had thinner cortex compared to healthy controls and conducted Pearson correlations with our behavioral measures (Table 6). Within the healthy control group, increased performance on category fluency related to increased social functioning, but social functioning did not relate to SFG cortical thickness. However, SFG cortical thickness did show a relationship with category fluency in the predicted direction; increased cortical thickness related to increased performance on the category fluency test. In the schizophrenia group, although this relationship was not significant, it was moderately sized in the predicted direction. No relationship between SFG and social functioning was observed in schizophrenia participants. Schizophrenia participants did show a trend level (p=0.059) relationship between increased performance on the CPT-IP and increased role functioning. No other relationships were identified in within group analyses. Across all participants, increased SFG cortical thickness related to increased role functioning, and showed a trend level (p=0.057) relationship with increased performance in category fluency. Increased category fluency also related to increased social functioning, but this was primarily driven by the healthy control group and social functioning did not relate to SFG cortical thickness.

Table 6. Correlations between cortical thickness in superior frontal gyrus and measures of attentional control and functioning

	SZ GROUP				**HC GROUP**				**ALL PARTICIPANTS**			
	SFG Thickness	Category Fluency	CPT	Role	SFG Thickness	Category Fluency	CPT	Role	SFG Thickness	Category Fluency	CPT	Role
Category Fluency	0.15	-			0.38*	-			**0.26**†	-		
CPT	0.05	-0.1	-		-0.05	-0.1	-		0.06	0.06	-	
Role	0.34	0.08	0.38†	-	0.28	0.27	0.33	-	**0.29***	**0.41***	0.21	-
Social	0.07	0.06	0.08	0.55**	0.30	0.42*	0.18	0.60**	0.18	0.41**	0.19	0.75**

Note: Bolded values indicate variable relationships entered into mediation analysis to test hypothesis three (see methods)
** $p < 0.001$; * $p < 0.05$; † trend level significant, $p = 0.06$

For mediation analysis to be justified, the predictor, mediator, and outcome variables must all be inter-related (MacKinnon, 2008). Because category fluency was the only cognitive control variable shown to relate to both SFG cortical thickness and functioning, and role functioning was the only functioning measure shown to relate to both SFG thickness and a measure of cognitive control (category fluency), we entered SFG cortical thickness, category fluency, and role functioning into a single mediator model to test our third hypothesis that cognitive control mediates the relationship between cortical thickness and functioning.

Hypothesis 3: Cognitive control will mediate the relationship between cortical thickness and functioning.

To test our third hypothesis we assessed a single mediator model in which cognitive control (as measured by category fluency) is postulated to mediate the relationship between cortical thickness in the SFG and role functioning. All four paths were in the predicted direction (Figure 3). SFG cortical thickness had a positive effect on role functioning (β=2.43, p=0.033) and cognitive control (β=80.79, p=0.057); cognitive control had a positive effect on role functioning (β=0.01, p=0.007). Bootstrap analysis of the indirect effect revealed a bias corrected confidence interval excluding zero (β=0.77; SE=0.55; $CI_{.95}$ = 0.09, 2.34), representing a medium effect size (κ^2=0.09; $CI_{.95}$ = 0.02, 0.23). Importantly, the direct effect of SFG cortical thickness on role functioning, controlling for cognitive control, was no longer significant (β=1.59, SE=1.08; p = 0.15) indicating that cognitive control abilities fully mediate the relationship between cortical thickness in the SFG and role functioning. The overall regression model with SFG cortical thickness and cognitive control as predictors of role functioning accounted for

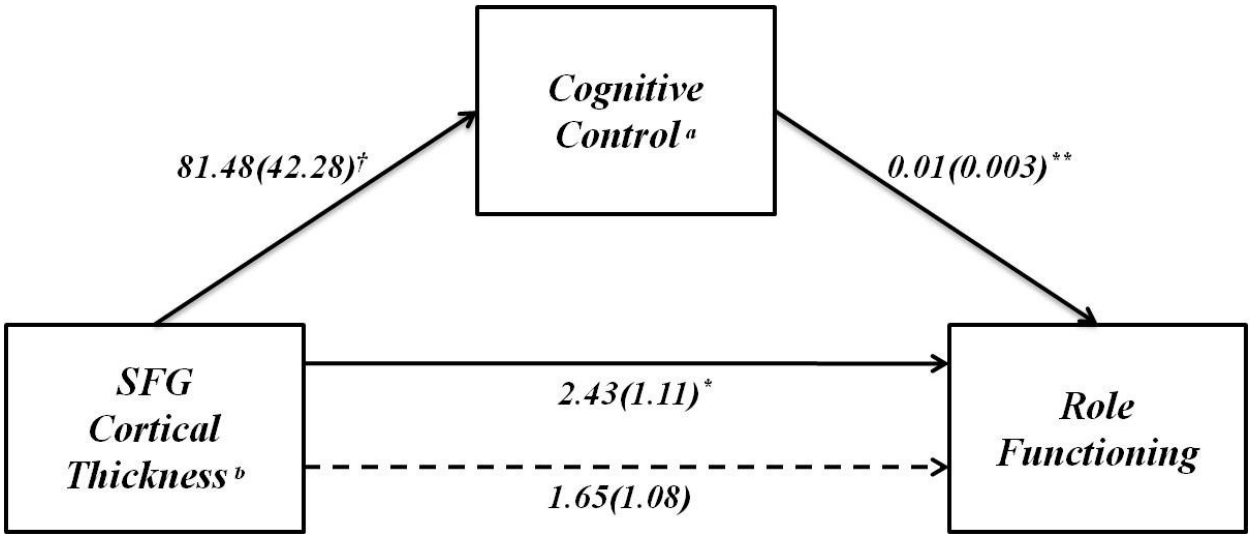

Figure 3. The effect of cortical thickness in the superior frontal gyrus on role functioning through cognitive control. When cognitive control was included in the model the direct effect of cortical thickness in the superior frontal gyrus on role functioning (dashed line) was no longer significant, indicating a fully mediated effect. Unstandardized path coefficients (SE) shown for each path. SFG = superior frontal gyrus. *p< 0.01; **p<0.05; †p=0.057; [a] Cognitive control was measured by the category fluency animal naming task. [b] Mean cortical thickness in the SFG for each participant was extracted from the cluster where group differences in cortical thickness was identified in whole brain vertex-by-vertex analysis in Freesurfer (see methods).

20% of the variance in role functioning ($F(2,52)=6.63$, $p=0.003$, $R^2=0.20$). The R^2 of the indirect effect size, R^2_{med}, (i.e. the variance in role functioning that is shared by SFG thickness and cognitive control) indicates that SFG cortical thickness and cognitive control share 5% of the variance in role functioning ($R^2_{med} = 0.05$, $CI_{95} = 0.05, 0.16$).

These results demonstrate that cognitive control abilities as measured by the category fluency task fully mediates the relationship between cortical thickness in the SFG and role functioning, indicating that cognitive control processes underlie the relationship between variations in neuroanatomical characteristics and behavioral variations in role functioning.

Discussion

Using surface based morphometry (SBM), this study examined differences in cortical thickness and surface area between healthy controls and individuals with schizophrenia, and how

SBM relates to behavioral measures of cognitive control, and social and role functioning. Three main findings emerged: first, SBM analysis identified a cluster in the superior frontal gyrus (SFG; BA10) where schizophrenia participants had reduced cortical thickness compared to healthy individuals. This replicates prior findings (Gutiérrez-Galve, et al., 2010; Janssen, et al., 2009; Schultz, et al., 2010) and provides further evidence that abnormalities in the cortical sheet, particularly in lateral/dorsomedial prefrontal regions are characteristic of schizophrenia. Second, decreased cortical thickness in this identified region of the SFG related to decreased role functioning, demonstrating a direct relationship between neurobiological characteristics of schizophrenia and functioning impairments directly observable in patients. Third, performance on the category fluency (animal naming) task - our proxy for cognitive control - fully mediated the relationship between cortical thickness in the SFG and role functioning, indicating that disease-related abnormalities in cortical thickness effect real-world functioning through impaired cognitive control processes.

These findings have implications for understanding the specific role of SFG abnormalities in role functioning impairments in schizophrenia. Here, we found schizophrenia participants to have reduced cortical thickness in a region of the SFG located in the anterior portion of the dorsomedial PFC (BA10). This region has been shown to be involved in a range of processes reliant on cognitive control, including set-switching (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999), working memory (Braver & Bongiolatti, 2002), and complex problem solving (Burgess, et al., 2000). Consequently, BA10 is primarily thought to implement higher-order control processes when multiple cognitive operations must be coordinated to respond appropriately to rapidly changing demands in environment in everyday life (Burgess, et al., 2000; Ramnani & Owen, 2004). Given that successful performance in the work or school

environment is reliant on these higher-order control processes in order to maintain context appropriate behavior and achieve desired/required goals, it seems intuitive that neural structure in this region impacts role functioning. Our finding that cognitive control fully mediates the relationship between cortical thickness in the SFG begins to illuminate *how* SFG cortical structure influences role functioning. Optimal performance on the category fluency task not only requires the directed retrieval of words from long-term memory, but also efficient set-switching, the maintenance in working memory of words already generated, and inhibition of irrelevant items (Henry & Crawford, 2004; Rende, et al., 2002); that is, processes reliant on overarching cognitive control mechanisms at least partly implemented in the SFG. Prior studies have shown category fluency predicts functional outcome in schizophrenia (Green, et al., 2004). Considered together, these observations indicate it is reasonable to postulate that cognitive control processes, reliant on SFG mechanisms, relate to role functioning. Our findings provide direct evidence to support this; the results from mediation analysis clearly demonstrate that cognitive control is one of the mechanisms underlying the relationship between cortical thickness in the SFG and role functional impairment.

This study adds to a growing body of literature linking the neural indicators of schizophrenia to the neurocognitive and clinical indicators of the disease. Several studies have shown relationships between executive or cognitive control tasks and neuroanatomical abnormalities in schizophrenia (Ho, et al., 2003; Minatogawa-Chang, et al., 2009; Seidman, et al., 1994; Zierhut, et al., in press), and functional neuroimaging studies are increasingly demonstrating a relationship between neural function to real-world behavior (e.g. Berkman, Falk, & Lieberman, 2011). Directly relevant to this study, Takizowa and colleagues (2008) found a relationship between activation in BA10 during category fluency tasks and global functioning;

moreover, LPFC connectivity during cognitive control and working memory tasks has been shown to predict global functioning (Sanz, et al., 2009; Yoon, et al., 2008). Our findings extend this literature to understanding the neurocognitive mediators that link brain to behavior, and demonstrate that the "brain-as-predictor" approach (Berkman, et al., 2011) can be extended from studies of neural function to meaningfully connect neuroanatomical indicators of psychological processes to behavior.

Study limitations must be acknowledged. Our identification of only one region of group-related differences in cortical thickness, and no group differences in surface area, are at odds with the literature; SBM studies tend to report multiple regions showing reduced/abnormal cortical surface characteristics (e.g. Schultz, et al., 2010). It is possible that we failed to detect real effects due to small sample size. Although our sample size is sufficient to detect medium sized differences (0.5 - 1mm differences in thickness), it is underpowered to detect small differences (e.g. <=0.25mm differences in thickness) between groups in temporal and limbic structures (Pardoe, Abbott, Jackson, & The Alzheimer's Disease Neuroimaging Initiative, 2012). Additionally, we may have failed to detect abnormalities in specific regions because we did not account for intersubject sulcal and gyral variations. For example, individual variation in the incidence of the paracingulate sulcus (PCS) affects the size of both the limbic and paralimbic anterior cingulate, thus failure to take PCS variation into account could obscure group differences (Fornito, et al., 2008). Finally, although social functioning was also related to the category fluency measure of cognitive control, we did not find a relationship between social functioning and cortical thickness in the SFG. Given the inherently affective nature of social interactions, it is possible that social functioning is more strongly related to prefrontal regions involved in affective processes, such as the ventrolateral prefrontal cortex (VLPFC), and that this

relationship is mediated by cognitive control of emotional information. In functional neuroimaging studies the VLPFC has been shown to relate to cognitive control of emotional information and social interactions in healthy individuals (Hooker, et al., 2010) and high risk samples (Hooker, et al., under review). Next steps include investigating the relationship between neuroanatomical abnormalities in the LPFC, cognitive control in relation to affective information, and social functioning.

Conclusion

This study combines surface-based morphometry methods and behavioral measures of cognitive control and role functioning to demonstrate a direct relationship between cortical thickness abnormalities and two characteristic deficits in schizophrenia. Results indicate that reduced cortical thickness in the superior frontal gyrus contributes to role functioning deficits in schizophrenia through impaired cognitive control. These findings provide insight into how the underlying neuroanatomical indicators of schizophrenia effect clinical and behavioral presentations of the illness.

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Paper #3: Lateral prefrontal cortex dysfunction during cognitive control of emotion predicts daily social experience in schizophrenia

Submitted for publication.

Authors

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Abstract

The neural basis of social impairment in schizophrenia is poorly understood. Cognitive control mechanisms, mediated by the lateral prefrontal cortex (LPFC), are known to influence response to interpersonal stressors in healthy individuals, thus impairments in these processes may contribute to social deficits. LPFC dysfunction is well documented in schizophrenia but no study has directly examined the relationship between LPFC dysfunction and real-world social interactions. This study investigated 1) whether schizophrenia participants show LPFC deficits during cognitive control of emotional information, and 2) whether these LPFC deficits prospectively predict experience sampling diary data of their daily social interactions. During fMRI, 23 individuals with schizophrenia or schizoaffective disorder and 24 demographically-matched healthy controls completed a standard cognitive control task superimposed on neutral and negative pictures. Afterwards, schizophrenia participants completed an online daily-diary in which they rated the extent to which they experienced or engaged in certain moods, thoughts, and social behaviors. Compared to healthy participants, schizophrenia participants had lower LPFC activity during cognitive control of task-irrelevant negative emotional information. Within schizophrenia participants, lower LPFC activation during control of negative emotional information was associated with less prosocial feelings and enjoyment of social interactions, more avoidance during interpersonal conflicts, and less resolution of interpersonal conflicts. This

study demonstrates a direct link between LPFC dysfunction and real-world social interactions in schizophrenia. Results suggest that compromised LPFC function may be a vulnerability that contributes to social deficits via impaired cognitive control of emotional information.

Introduction

Social functioning deficits are a core, debilitating, and treatment refractory feature of schizophrenia (Couture, et al., 2006; Harvey & Bellack, 2009). Social interactions by nature involve affectively salient information, particularly interpersonal conflicts, which can be emotionally challenging and require regulation of negative affect and behavior for successful resolution (Arriaga & Rusbult, 1998; Lopes, et al., 2011). Impairments in these self-regulatory mechanisms, reliant on cognitive control processes mediated by the lateral prefrontal cortex (LPFC; Heatherton & Wagner, 2011; Ochsner, Silvers, & Buhle, 2012), may be especially important in the development and persistence of social impairments. LPFC dysfunction, particularly during cognitive control tasks, is a well-established neural impairment in schizophrenia (Barch, 2005; Manoach, 2003; Minzenberg, et al., 2009), and may be a biomarker for the illness (Lesh, et al., 2011; Woodward, et al., 2009). However, there is a paucity of research examining the social consequences of LPFC deficits. Without evidence directly tying LPFC dysfunction to core characteristics of illness, including social deficits, its usefulness as a biomarker remains unclear. One proposal is that LPFC dysfunction is a biological vulnerability that, in the presence of an interpersonal stressor, contributes to social impairments via impaired cognitive control of emotional information (Hooker, et al., 2010; Kring & Werner, 2004). The current study seeks to directly tie laboratory based measures of LPFC activity during cognitive control of emotional information to social interactions and daily functioning in schizophrenia.

LPFC, comprising both dorsolateral (DLPFC) and ventrolateral (VLPFC) regions, is consistently implicated in laboratory assessed cognitive control of emotional information (Ochsner & Gross, 2005; Ochsner, et al., 2012; Pessoa, 2008), and response to interpersonal stressors may be mediated by LPFC function. Lower VLPFC activity during social exclusion

predicts higher self-reported distress (Eisenberger, et al., 2003). Similarly, lower VLPFC activity when viewing negative facial expressions predicts increased negative mood and maladaptive behavior following interpersonal conflicts (Hooker, et al., 2010). In schizophrenia, interpersonal conflicts, especially conflicts characterized by criticism, predict symptom exacerbation and higher relapse rates (Hooley, 2007). Moreover, symptom exacerbation in response to interpersonal criticism is related to poor working memory and cognitive control (Rosenfarb, Nuechterlein, Goldstein, & Subotnik, 2000), neurocognitive processes known to be mediated by the LPFC (Aron, Robbins, & Poldrack, 2004; Curtis & D'Esposito, 2003) and to predict functional outcome (Milev, et al., 2005). Collectively, these data suggest that compromised LPFC function is a vulnerability for symptom exacerbation and functional difficulties in response to interpersonal conflict. However, research attempting to connect LPFC activity to interpersonal interactions in schizophrenia is sparse. To date, studies have primarily focused on the relationship between the LPFC and symptoms. Findings show a consistent pattern of LPFC dysfunction relating to increased symptoms (Goghari, et al., 2010; MacDonald, et al., 2005; Menon, et al., 2001; Nishimura, et al., 2011; Perlstein, et al., 2001; van Veelen, et al., 2010) and normalization of function relating to decreased symptoms (Edwards, et al., 2010; Fusar-Poli, Broome, et al., 2011), clearly indicating a direct link between LPFC pathophysiology and symptomatology of schizophrenia. However, to our knowledge, only two studies have reported a relationship between LPFC activity and functioning. Both found reduced LPFC connectivity within fronto-parietal networks during a cognitive control task related to impairments on global measures of functioning (Sanz, et al., 2009; Yoon, et al., 2008). However, global measures of functioning incorporate many aspects of behavior into a single aggregate score, thus the specific role of LPFC in controlling social and emotional responses to interpersonal stressors remains

unclear. The scarcity of findings directly linking LPFC function to social deficits may result from limitations inherent in the currently available and commonly used methods.

First, the tasks traditionally used to assess LPFC function, such as response inhibition or working memory tasks (Barch, 2005), although robust activators, may not be the most sensitive measures for assessing how LPFC activity relates to real-world social functioning because they do not directly capture cognitive control of emotional information. Given the inherently affective nature of social interactions and the accompanying need for self-regulation (Arriaga & Rusbult, 1998), tasks assessing the *interaction* between LPFC mediated cognitive control and emotional information may provide a more accurate reflection of the inhibitory demands of real-world social contexts. Indeed, evidence suggests that LPFC mediated control of emotional information underlies the facilitation and regulation of emotions, as well as their translation into goal-directed behaviors (Ochsner & Gross, 2005). By using "cold cognitive" tasks and not assessing LPFC mediated cognitive control in relation to emotional information, previous studies may have lacked the sensitivity necessary to identify the role of LPFC dysfunction in social impairments.

Second, prior research has primarily assessed symptoms and functioning using laboratory-based one-time retrospective measures. Although these provide an overview of an individual's general level of functioning, they are not well-suited for capturing the multidimensional nature of social interactions in daily life, and rarely provide the context in which they occur (Trull & Ebner-Priemer, 2009). Social interactions do not occur in a vacuum; day-to-day changes in social behavior may be prompted at a specific time, in a specific setting, or in the context of a particular interpersonal relationship. One-time retrospective evaluations of social functioning miss these nuances, calling into question their ecological validity (Yager & Ehmann, 2006), and potentially explaining the lack of findings directly tying LPFC deficits to

social impairments. Experience Sampling Methods (ESM), considered to be a more ecologically valid assessment of social functioning, have revealed a nuanced relationship between changes in the social environment, particularly social stressors, and symptoms (Myin-Germeys, et al., 2009; Oorschot, Kwapil, Delespaul, & Myin-Germeys, 2009), leading to the proposal that impaired ability to control emotional information in the context of social stress reflects an affective pathway to psychotic symptoms (Myin-Germeys & van Os, 2007). This is consistent with the proposal that impaired cognitive control of emotional information contributes to social deficits (Hooker, et al., 2010; Kring & Werner, 2004) and suggests that using ESM in conjunction with neuroimaging techniques may provide a more sensitive and ecologically valid approach to understanding the contribution of LPFC dysfunction to social deficits in schizophrenia.

The present study addressed these limitations by combining fMRI and ESM to test whether people with schizophrenia have LPFC deficits in cognitive control of negative emotional information, and, if so, whether LPFC deficits are related to worse daily mood, symptoms, and social functioning. Individuals with schizophrenia and demographically-matched healthy controls completed an adapted version of the Multi-Source Interference Task (MSIT), a cognitive control task specifically designed to robustly activate the cingulo-frontal-parietal cognitive control network by combining the classic inhibitory demands of the Flanker and Simon interference effects (Bush & Shin, 2006). In our adapted version, the MSIT-Emotion, MSIT stimuli are superimposed on a negative emotional scene (e.g. an injured woman being carried from a burning building) that is irrelevant to the central task demand. Thus, rather than requiring explicit manipulation of emotional material, the task requires participants to inhibit the effect of irrelevant emotional information presented in the external environment on task performance, a process thought to more accurately reflect the interaction of emotion and cognitive control in

real-world social contexts (Silbersweig, et al., 2007). Our measure of cognitive control of emotion was LPFC activity when inhibiting the effect of irrelevant emotional information during high interference trials (when cognitive control skills are most challenged) relative to no interference trials. Stimuli were also superimposed on neutral pictures, included to test the specificity of schizophrenia participants' LPFC deficits for controlling emotional information. To avoid confounding group differences in fMRI data with behavioral performance differences, participants were required to demonstrate on practice trials prior to entering the scanner. Following the scan, schizophrenia participants completed an online, structured daily-diary questionnaire every evening for three weeks. End-of-the-day reports provide data on day-to-day fluctuations in behavior whilst minimizing interference with participants' daily experience. Participants rated the extent to which they experienced or engaged in certain moods, thoughts, and social behaviors. Given the importance of interpersonal stressors in symptomatology and course of illness (Hooley, 2007), diary items assessing social functioning predominantly focused on the occurrence and response to interpersonal conflict. Laboratory-based measures of symptoms and functioning were collected to corroborate the daily-diary data. Based on findings from our previous study examining LPFC mediated cognitive control of emotional information in relation to interpersonal conflict, we anatomically defined the LPFC as the bilateral middle and inferior frontal gyri (Hooker, et al., 2010). We hypothesized: 1) schizophrenia participants would show reduced LPFC activity during cognitive control of emotional information compared to healthy participants; 2) schizophrenia participants would show cognitive control-related neural deficits specific to the inhibition of negative emotional material during high interference trials; 3) Among schizophrenia participants, LPFC activity during cognitive control of emotional

information will predict mood, symptoms, social behavior, and response to interpersonal conflict in daily life.

Methods

Participants

23 individuals with schizophrenia or schizoaffective disorder and 24 healthy controls were recruited from the Greater Boston area. Groups were matched for gender, age, education, and IQ (Table 7). Inclusion criteria for all participants: age 18-65, primary English speaker, no neurological or major medical illness, no head trauma history, no substance abuse within six months, no current/past substance dependence. Inclusion criteria for schizophrenia participants: diagnosis of schizophrenia or schizoaffective disorder, no comorbid axis I disorders, no history of electroconvulsive therapy. Inclusion criteria for healthy participants: no current/past axis I disorders, no first-degree relative with a psychotic disorder, scores within 1.5 standard deviations of the population mean on five measures schizotypal personality (perceptual aberration scale (Chapman, Chapman, & Raulin, 1978), magical ideation scale (Eckblad & Chapman, 1983), referential thinking scale (Lenzenweger, et al., 1997), physical anhedonia scale (Chapman, et al., 1976), revised social anhedonia scale (Eckblad, et al., 1982)). Psychopathology was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First, et al., 2002); symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Opler, & Fiszbein, 1987). Standard measures of social functioning included the Global Functioning: Social scale (GFS; Auther, et al., 2006) and Social Adjustment Scale-Self-Report (SAS-SR; Weissman, et al., 1978) (see appendix for supplemental methods). Clinical assessments were conducted by trained PhD-level clinical psychologists (LMT, SHL) supervised by a licensed clinical psychologist (CIH).

Table 7. Demographics and behavioral data

	SZ Group	Control Group	Differences Between Groups
N	23	24	
Gender: (M/F)	14/9	15/9	$\chi 2$ (1) = 0.013, p = 0.91
Age	39.3 (9.60) [21-58]	34.54 (12.23) [19-55]	t(45)= 1.481, p = 0.15
Education	14.78 (2.19) [10-18]	14.62 (2.84) [11-21]	t(45) = 0.212, p = 0.83
IQ	108.35 (14.14) [82-133]	111.29 (11.44) [88-130]	t(45) = 0.786, p = 0.44
Diagnosis [b]			
Schizophrenia N (%)	17 (74%)		
Schizoaffective N (%)	6 (26%)		
Age of Illness Onset	21.64 (4.55) [13-30]		
Antipsychotic Medication [c]			
Atypical N (%)	16 (70%)		
Typical N (%)	3 (13%)		
None N (%)	3 (13%)		
CPZ Equivalent [d]	394.20 (395.80) [0-1600]		
PANSS symptoms			
Positive	16.26 (5.69) [7-30]		
Negative	13.35 (5.69) [7-27]		
Disorganized	8.13 (4.39) [5-18]		
Social Functioning:			
Social Adjustment Scale - Social & Leisure T score	63.70 (16.05) [36-98]	48.79 (6.93) [36-66]	t(45) = 4.163, p < 0.001, *d* = 1.24[e]
Global Functioning: Social Scale	6.00 (1.78) [3-9]	8.58 (1.32) [6-10]	t(45) = 5.667, p < 0.001, *d* = 1.69
MSIT-Emotion Behavioral Data[e]			
RT mean (*msec*), (SD)			
Neutral Control	843.45 (134.25)	783.89 (111.75)	t(43) = 1.62, p = 0.11
Neutral Interference	1046.39 (128.50)	1012.14 (117.33)	t(43) = 0.93. p = 0.36

Table 7. Demographics & Behavioral Data (Continued)

	SZ Group	Control Group	Differences Between Groups
Within Group Interference Effect	Int > Con; t(20) = 12.24, p < 0.001	Int > Con; t(23) = 18.98, p < 0.001	
Negative Control	872.93 (125.99)	819.97 (121.35)	t(43) = 1.44, p = 0.16
Negative Interference	1059.84 (116.09)	1050.97 (135.04)	t(43) = 0.24, p = 0.82
Within Group Interference Effect	Int > Con; t(20) = 13.72, p < 0.001	Int > Con; t(23) = 22.85, p < 0.001	
Accuracy (%), (SD)			
Neutral Control	98.51 (2.10)	98.26 (4.46)	t(43) = 0.23, p = 0.82
Neutral Interference	96.43 (5.67)	93.58 (7.03)	t(43) = 1.48, p = 0.15
Within Group Interference Effect	Con > Int; t(20) = 1.81 p = 0.09	Con > Int; t(23) = 4.23, p < 0.001	
Negative Control	97.82 (2.67)	97.40 (3.95)	t(43) = 0.41, p = 0.68
Negative Interference	93.15 (8.59)	93.32 (9.28)	t(43) = 0.60, p = 0.95
Within Group Interference Effect	Con > Int; t(20) = 2.61 p = 0.02	Con > Int; t(23) = 2.55, p = 0.02	

Note: data represent mean (SD), [range] unless otherwise indicated. Due to technical problems, behavioral data for the MSIT-Emotion was not collected for two SZ participants. [a] Full scale IQ scores were estimated using the vocabulary and matrix reasoning subtests of the Weschler Abbreviated Scale of Intelligence (WASI); [b] Subtypes of the 17 participants with schizophrenia were: 13 Paranoid, 3 Residual, and 1 Undifferentiated. Subtypes of the 6 participants with Schizoaffective disorder were: 3 Bipolar, and 3 Depressive; [c] One patient did not report medication; [d] CPZ = Chlopromazine equivalents calculated using methods described in Woods (2003) [e] Cohen's d effect size.

Harvard University Institutional Review Board approved the study. Participants gave written informed consent and were paid for their participation. Participants completed behavioral assessments, returned a separate day for the scan, and were subsequently oriented to the daily-diary.

fMRI

fMRI Task: MSIT-Emotion. Cognitive control of emotional information was assessed with the MSIT-Emotion (Figure 4), an adaptation of the MSIT, a standard cognitive control paradigm that combines the Flanker (Eriksen & Eriksen, 1974) and Simon (Simon & Berbaum, 1990) effects to robustly activate the cingulo-frontal-parietal cognitive control network within individual subjects (Bush & Shin, 2006). In the MSIT, subjects see sets of three numbers (1,2, or 3) and report the identity of the number that differs from the other two. During control trials, position of the target number is always congruent with its position on the button box and the other two 'distracter' numbers are zeros; thus there is no spatial or semantic interference. During interference trials, position of the target number is incongruent with its position on the button box and the distracters are other numbers. This creates two sources of interference: spatial incongruence between the target and response (Simon effect) and semantic incongruence between the target and distracter numbers (Flanker effect). In the MSIT-Emotion, task stimuli (i.e. the numbers for interference and control trials) are shown on a background of either a neutral or negative picture, resulting in four conditions: neutral control (NeuCon), neutral interference (NeuInt), negative control (NegCon), and negative interference (NegInt). 48 neutral pictures and 48 negative pictures were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005) (see appendix for supplemental methods).

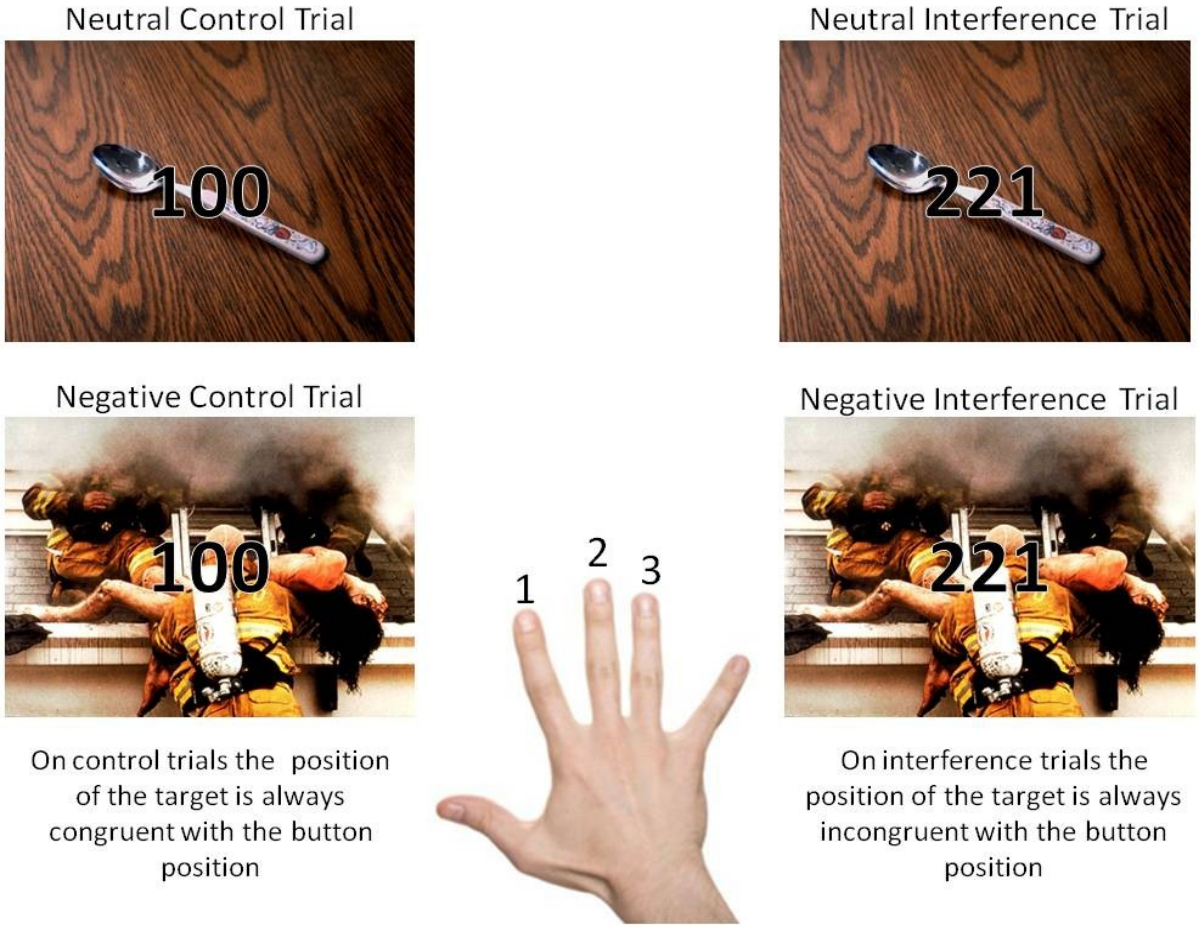

Figure 4. The MSIT-Emotion. The MSIT-Emotion is presented in an event-related design format. Control and interference trials are presented on a background of either a neutral or negative picture for 1.75 seconds followed by a variable inter-trial interval (central fixation cross) of 4-10 seconds. Participants see sets of three numbers and are required to report the identity of the number that is different from the other two. During control trials the position of the target number is always congruent with its position on the button box, and distracter numbers are always zeros. During interference trials the position of the target number is always incongruent with its position on the button box and distracter numbers are other numbers (either 1, 2, or 3). In all examples shown, the correct answer would be to press the button "1" with the index finger.

Trials were presented in an event-related design so that correct and incorrect trials could be analyzed separately. Each trial was presented for 1.75 seconds followed by a variable inter-trial interval (central fixation-cross) for 4-10 seconds. Pictures were randomly assigned to conditions; trial types were presented in a fixed, pseudo-random order.

Before entering the scanner, participants completed a practice version of the task (10 trials for each of the 4 conditions). Participants were required to achieve 80% accuracy or higher before entering the scanner to ensure task competency; thus any group differences would not be due to task difficulty/performance differences. All participants reached 80% accuracy on their first practice. After the scan, participants rated the valence of each neutral and negative picture (see supplemental methods).

fMRI Single-Subject Analysis. Images were acquired on a Siemens 3T TimTrio scanner and analyzed using SPM8 within the general linear model (GLM) framework. For single-subject GLMs, vectors of onset times with 0s duration were defined for each event in each condition (NeuCon, NeuInt, NegCon, NegInt) and convolved to the canonical HRF with a high pass frequency filter of 128s. Artifact detection and movement correction was conducted using the Artifact detection tools software package (ART; Whitfield-Gabrieli, 2009). Regressors were created to exclude volumes with gross motion (>3mm relative to previous time frame) or spiking artifacts (global mean image intensity greater than 3SD from the mean of the entire time series within a scan) from analysis. There were no group differences in number of outliers identified (SZ max=30; HC max=28). Contrasts were calculated for each of the four conditions relative to fixation periods, and for interference versus control for neutral and negative pictures (i.e. NeuInt>NeuCon; NegInt>NegCon). See supplemental methods for further details of image acquisition, processing, and analysis.

fMRI Group Analysis.

Hypothesis 1: Schizophrenia participants have LPFC deficits in cognitive control of emotional information

We tested our central hypothesis that compared to healthy controls (HC), schizophrenia (SZ) participants would show reduced LPFC activity during cognitive control of emotional information using a 2x2 full factorial ANOVA with group (HC/SZ) and condition (NegInt/NegCon) as factors. The predicted group*condition interaction was that HC would have greater activity than SZ when inhibiting irrelevant negative emotional information on interference trials (NegInt) compared to inhibiting irrelevant negative emotional information on control trials (NegCon). Clusters showing the predicted group*condition interaction within the LPFC (anatomically defined as middle and inferior frontal gyri) were identified and contrast values for each condition for each subject were extracted from the peak voxel. The difference between NegInt and NegCon (NegInt-NegCon) was calculated and used in the analysis with the daily-diary data.

LPFC deficits in schizophrenia are hypothesized to be most apparent when controlling the influence of irrelevant emotional information; thus, we did not expect a between-group difference for neutral interference relative to neutral control. This was examined with a 2x2 ANOVA with factors group (HC/SZ) and condition (NeuInt/NeuCon).

Hypothesis 2: Schizophrenia participants have neural deficits specific to inhibiting negative emotional information on interference trials

We tested whether schizophrenia participants have an exaggerated deficit when inhibiting negative emotional information during interference trials whilst accounting for activity when inhibiting negative emotional information during control trials and neutral information on

interference trials. This was examined with a 2x2 full factorial ANOVA with the contrasts NegInt>NegCon and NeuInt>NeuCon entered for the condition factor. We investigated regions showing a group*condition interaction in which HC have greater activity than SZ for NegInt>NegCon relative to NeuInt>NeuCon. Because we expect basic cognitive control skills (recruited for the neutral interference trials) to contribute, somewhat, to effective social functioning, we did not use activity from this analysis to predict daily-diary ratings.

Group maps were thresholded at $t=3.18$, $p<0.001$ (uncorrected) with 10 voxels/270mm cluster size; for completeness, all BOLD activation above this threshold is reported in the tables. Clusters surviving whole brain corrections using Family Wise Error correction (FWE, $P<0.05$) are highlighted. Additionally, small volume corrections using FWE ($p<0.05$) were conducted for cognitive control related regions where suprathreshold clusters were detected. WFU pickatlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) was used to create anatomically defined masks for LPFC (specified as bilateral middle and inferior frontal gyri), bilateral superior frontal gyri, bilateral lateral orbital gyri, and bilateral amygdala.

The Daily-Diary

The daily-diary consisted of a structured questionnaire completed online at the end of each day (i.e. 'right before bed') for 21 consecutive days. Diary questions focused on quality and quantity of social interactions. Schizophrenia participants reported whether or not they had specific types of social interactions (e.g. face-to-face, email, etc.), the extent to which they experienced the interactions as rewarding, and experienced prosocial feelings (e.g. felt friendly and accepted). Participants also reported whether they had an interpersonal conflict (yes/no), and if so, the extent to which the conflict caused distress, was resolved, and included engagement in maladaptive strategies (e.g. anger or avoidance). Participants also rated their level of positive,

negative, and disorganized symptoms, depression, anxiety, irritability, cognitive confusion, and positive mood. Questions were rated on a 1-to-5 scale (1=not at all; 5=extremely). The dependent measure for each daily-diary variable was the average response from 1-5 diary questions. See Supplemental Tables 1 and Supplemental Table 2 in appendix for full list of diary items.

Hypothesis 3: LPFC deficits during cognitive control of emotional information predicts social functioning and symptoms

Daily-diary data was used to test the hypothesis that schizophrenia participants' LPFC deficits in cognitive control of emotional information are related to worse symptoms and social functioning. LPFC deficits were identified as the LPFC region where schizophrenia participants had less activity than healthy controls for NegInt relative to NegCon. Results from the fMRI analysis revealed a cluster with peak (x=-39, y=20, z=40) located in the middle frontal gyrus BA 46/9. Contrast values from each condition were extracted from the peak and the difference between each condition was calculated (NegInt-NegCon). This difference score was then used to predict schizophrenia participants' daily social experiences and symptoms. To corroborate daily-diary data, bivariate Pearson correlations were conducted between this difference score and laboratory-based measures of social functioning and symptoms.

The diary data has a hierarchical structure where days are nested within participants. Thus, we used a hierarchical linear modeling (HLM) approach with the mixed procedure in SAS. Lower-level (*within-person)* analyses generated independent estimates of each participant's average level of a diary variable (e.g. average prosocial feelings across 21-days). Collecting repeated assessments every day for 21-days provides a highly reliable estimate of that individual's symptom or social behavior. We then examined whether the between-subject

variable, LPFC activity during the control of negative emotional information (NegInt-NegCon), predicted their average daily experience across the 21-day diary period.

Twenty schizophrenia participants completed the daily-diary. Laptop computers were provided for participants without internet access. Staff sent phone/email reminders each evening and monitored entries. Compliance was high (missed days: mean=1.1, SD=1.8; range:0-6).

Results

Behavioral. The MSIT-Emotion elicited expected interference effects (Table 7). All participants responded slower and were less accurate on interference trials compared to control trials; participants also responded slower on negative picture trials compared to neutral picture trials. There were no group differences in reaction time or accuracy.

fMRI Task Validation. One sample t-tests of NeuInt>NeuCon and NegInt>NegCon confirmed that the MSIT-Emotion activates the expected cognitive control network. Both HC and SZ participants demonstrated task-related activity in cognitive control regions including inferior and middle frontal gyri (LPFC), superior frontal gyrus (Dorsomedial PFC), and anterior cingulate cortex (ACC) (Figure 5; Supplemental Table 3 and Supplemental Table 4 in appendix).

fMRI Group Analysis.

Hypothesis 1: Schizophrenia participants have LPFC deficits in the cognitive control of emotional information

The group*condition interaction testing inhibition of negative emotional information on interference trials compared to inhibition of negative emotional information on control trials

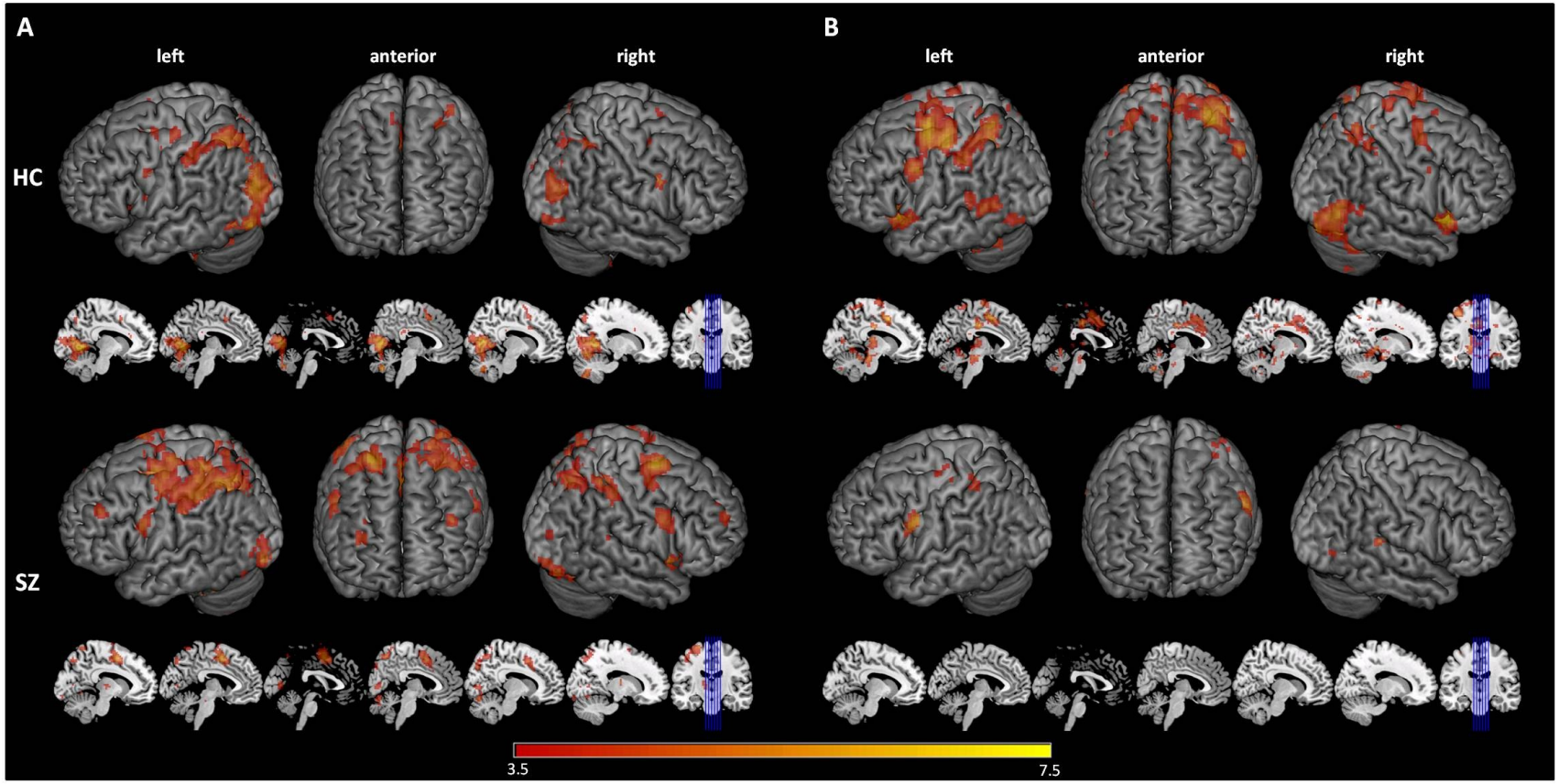

Figure 5. MSIT-Emotion Within-Group Interference Effect Related fMRI BOLD responses
A, One sample t-tests in neutral picture conditions (NeuInt – NeuCon) in both HC and SZ groups. B, One sample t-tests in negative picture conditions (NegInt – NegCon) in both HC and SZ groups. HC group results are displayed on the top row; SZ group results are displayed on the bottom row. 3D renderings are displayed in left, right, and anterior views alongside sagittal slices of an averaged MNI structural volume. Slices were chosen to focus more directly on midline and subcortical structures; slice numbers from left to right are: -10, -6, 0, 4, 10, 14. Coronal view of slice location is provided for reference. Neural activity clusters are based on one sample t-tests within each group with a significance threshold of $p < 0.001$ uncorrected and cluster threshold of 10 voxels/270mm.

showed a significant group*condition interaction (HC>SZ) in cognitive control regions (Table 8), including the left middle frontal gyrus (LPFC), bilateral superior frontal gyri (DMPFC), bilateral lateral orbital gyri (LOFC) extending into the anterior insula, bilateral dorsal ACC, and right amygdala. Clusters showing the predicted group*condition interaction within cognitive control regions are shown in Figure 6A. Figure 6A barplots illustrate that, in both the LPFC and LOFC, HC participants consistently demonstrate the expected pattern of activation: increased activation in NegInt compared to NegCon conditions; SZ participants show the opposite pattern, deactivating in NegInt compared to NegCon conditions.

Activation in the lateral orbital gyri (LOFC) survived whole brain correction (FWE, $p<.05$). Activation in the amygdala survived small volume correction. No other clusters survived corrections for multiple comparisons in this contrast.

The cluster in the middle frontal gyrus (peak: -39, 20, 40) was the only cluster within our LPFC region of interest mask. All subsequent analyses investigating LPFC activity and social functioning were conducted using the difference score NegInt-NegCon (i.e. our measure of cognitive control of emotional information) calculated from the contrast values in each condition extracted from the peak of that cluster.

No regions showed an interaction in the opposite direction (i.e. SZ>HC).

The group*condition interaction testing group differences for NeuInt versus NeuCon (HC>SZ; NeuInt>NeuCon) revealed no group differences. No regions showed an interaction in the opposite direction (i.e. SZ>HC; Table 8).

Hypothesis 2: Schizophrenia participants have neural deficits specific to inhibiting negative emotional information on interference trials

The group*condition interaction testing the inhibition of the negative picture whilst accounting for both the negative picture and the interference effect (i.e. HC>SZ; NegInt-NegCon>NeuInt-NeuCon) showed a significant group*condition interaction (HC>SZ) in the right superior frontal gyrus (DMPFC) and right lateral orbital gyrus (LOFC); activity remained significant after small volume correction (FWE, $p<0.05$). In both regions, HC participants demonstrated increased interference effect related activation in the negative picture conditions compared to neutral picture conditions; SZ participants showed the opposite pattern (Figure 6B).

No regions showed an interaction in the opposite direction (i.e. SZ>HC; Table 9).

Hypothesis 3: LPFC deficits during cognitive control of emotional information predicts social functioning and symptoms

Bivariate Pearson correlations across all participants revealed a significant relationship between LPFC activity and self-reported social functioning. Follow-up analyses showed no relationship between LPFC activity and social functioning in healthy individuals (all Ps>0.1). However, consistent with our hypothesis, lower LPFC activity related to lower social functioning in schizophrenia participants on both SAS-SR and GF:S (Table 10).

We used HLM to investigate whether LPFC activity during cognitive control of emotional information predicts daily social experiences in schizophrenia participants. LPFC activity did not predict the number of social interactions or the number of interpersonal conflicts. Consistent with our hypothesis, LPFC activity did predict the quality of social interactions. Schizophrenia participants with lower LPFC activity had less prosocial feelings (i.e. they felt less friendly, less accepted, and lonelier). When they did socialize, they experienced less enjoyment. Furthermore, although schizophrenia participants with low LPFC did not experience more

interpersonal conflicts, when they did have a conflict, they were more likely to avoid the person or issue and the conflict was less resolved at the end of the day (Table 11).

Schizophrenia participants with lower LPFC activity also had worse symptoms. Lower LPFC activity was related to higher levels of paranoia, depression, anxiety, irritability and cognitive confusion, and lower levels of positive mood.

Table 8. MSIT-Emotion group * condition interactions from 2x2 full factorial ANOVAs

Region	Brodmann Area	Peak MNI coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
Neutral picture Conditions						
Group (HC > SZ) x condition (NeuInt > NeuCon) interactions		No suprathreshold activity				
Group (SZ >HC) x condition (NeuInt > NeuCon) interactions		No suprathreshold activity				
Negative picture conditions						
Group (HC > SZ) x condition (NegInt > NegCon) interactions						
*R dorsal anterior cingulate**	24	12	-1	37	6.23	338/9126
R inferior parietal lobule*	48	30	-22	34	5.44	
R postcentral gyrus*	6	30	-7	34	5.10	
*R lateral orbital gyrus**	47	48	26	-14	5.64	262/7074
L insula*	48	-24	2	25	5.57	847/22869
*L lateral orbital gyrus**	47	-36	23	-11	5.54	
L dorsal anterior cingulate	24	-15	-7	34	4.79	
R posterior cingulate gyrus	31	15	-40	28	4.91	169/4563
L posterior cingulate gyrus	31	-21	-34	46	4.69	
L posterior cingulate gyrus[a]	31	-15	-49	31	4.25	
L posterior cingulate gyrus	31	-24	-25	34	4.49	26/702
L inferior parietal lobe	40	-33	-28	31	3.74	
L cerebellum	NA	-39	-58	-38	4.48	167/4509
L posterior cerebellum	NA	-36	-76	-32	4.42	
L posterior cerebellum	NA	-27	-82	-35	4.00	
R cerebellum	NA	33	-76	-38	4.47	148/3996
R cerebellar tonsil	NA	36	-58	-47	4.17	
R posterior cerebellum	NA	42	-55	-41	3.97	

Table 8. MSIT-Emotion group * condition interactions from 2x2 full factorial ANOVAs (Continued)

Region	Brodmann Area	Peak MNI coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
L middle temporal gyrus	37	-66	-49	-11	4.44	32/864
L cerebellum	NA	-48	-40	-29	4.43	135/3645
L inferior temporal gyrus	20	-63	-25	-17	4.16	
L middle temporal gyrus	20	-54	-31	-11	4.10	
L pons	NA	-6	-19	-17	4.42	47/1269
L pons	NA	-6	-28	-26	3.87	
R hipppocampus	NA	33	-16	-11	4.35	69/1863
R parahippocampal gyrus	NA	21	-22	-17	4.19	
R substantia nigra	NA	15	-19	-5	3.95	
L angular gyrus	39	-54	-61	28	4.28	94/2538
L supramarginal gyrus	39	-51	-46	28	3.77	
R cerebellum	NA	6	-52	-47	4.27	39/1053
R posterior cerebellum	NA	18	-49	-47	4.16	
R amygdala[b]	NA	27	-1	-17	4.26	61/1647
R putamen	NA	18	11	-5	3.88	
R insula	48	24	17	-11	3.74	
L superior frontal gyrus	6	-6	17	64	4.23	103/2781
L superior medial gyrus	8	-3	32	61	3.74	
L anterior cerebellum	NA	-15	-46	-17	4.10	15/405
L precuneus	5	-6	-40	70	4.09	42/1134
L superior temporal gyrus	21	-36	-46	10	4.08	18/486
L middle temporal gyrus	37	-39	-46	1	3.80	
L rostral anterior cingulate[b]	32	-6	41	13	4.06	74/1998
R anterior cerebellum	NA	24	-40	-29	4.00	23/621
R vermis	NA	18	-37	-20	3.70	
L parahippocampal gyrus	NA	-30	-22	-20	3.88	17/459
L parahippocampal gyrus	NA	-24	-25	-14	3.76	
L medial orbitofrontal cortex	11	-6	65	-8	3.75	10/270

Table 8. MSIT-Emotion group * condition interactions from 2x2 full factorial ANOVAs (Continued)

Region	Brodmann Area	Peak MNI coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
R superior frontal gyrus	9	15	53	37	3.68	34/918
R superior frontal gyrus	9	27	53	37	3.58	
L middle frontal gyrus	46/9	-39	20	40	3.51	18/486
L medial orbitofrontal cortex	11	-30	44	-8	3.52	15/405
L medial orbitofrontal cortex	11	-24	44	1	3.42	
R precentral gyrus	4	12	-25	73	3.51	18/486
R precentral gyrus	6	21	-28	67	3.50	
Group (SZ > HC) x condition (NegInt> NegCon) interactions	No suprathreshold activity					

Effects are reported with a significance threshold of $p < 0.001$ uncorrected and cluster threshold of 10 voxels/270mm. Clusters that include cognitive control regions are italicized. Neuroanatomical labels, MNI coordinates, and t-values are listed for the peak voxel of each cluster. Where multiple peaks exist, primary peaks and cluster sizes are reported first and neuroanatomical labels and MNI coordinates of sub-clusters are shown indented. Regions indicated with an asterisk survived whole brain correction for multiple comparisons (FWE, $p < 0.05$). Regions indicated with a superscript survived small volume correction (FWE, $p < 0.05$) applied to our a priori regions of interest : (a) includes voxels in anatomically defined bilateral cingulate cortices; (b) includes voxels in anatomically defined bilateral amygdala.

Figure 6. fMRI BOLD Responses Associated with Cognitive Control of Negative Emotion in HC vs. SZ groups.

Activation patterns and contrast estimates with group * condition interaction effects in our regions of interest are shown. A, The Negative Interference (NegInt) condition was compared with the Negative Control (NegCon) condition for HC and SZ participants. Significant interactions were observed in: (a) Left LPFC; (b) Left Lateral Orbital Gyrus; and (c) Left Dorsomedial PFC. B, The NegInt>NegCon contrast was compared with the NeuInt>NeuCon contrast for HC and SZ participants. Significant interactions were observed in: (a) Right Superior Frontal Gyrus; and (b) Right Lateral Orbital Gyrus. Contrast estimates were extracted from the peak voxel of the cluster and plotted for each group and each condition. All results shown above are based on full factorial 2x2 ANOVA implemented in SPM8, with a significance threshold of $p < 0.001$ uncorrected and a cluster threshold of 10 voxels/270mm.

Figure 6. fMRI BOLD Responses Associated with Cognitive Control of Negative Emotion in HC vs. SZ groups (Continued)

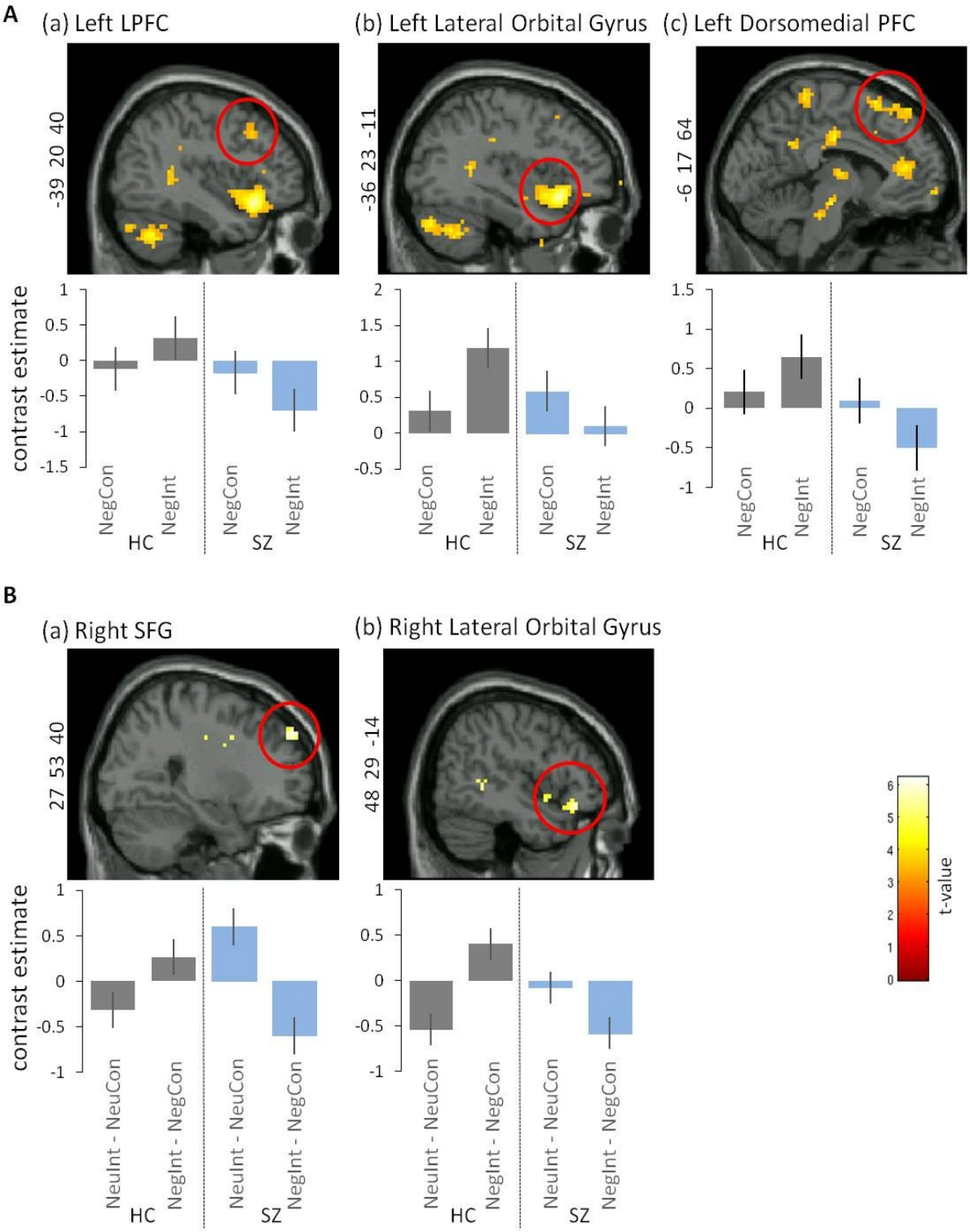

Table 9. MSIT-Emotion group * condition interactions from 2x2 full factorial ANOVA

Region	Brodmann Area	Peak MNI coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
Group (HC > SZ) x condition (NegInt vs. NegCon > NeuInt vs. NeuCon) interactions						
R superior frontal gyrus[a]	9	27	53	40	4.37	48/1296
R paracentral lobule	4	9	-31	73	4.31	40/1080
L cerebellar tonsil	NA	-36	-55	-41	4.08	15/405
R lateral orbital gyrus/LOFC[b]	47	48	29	-14	4.06	42/1134
R temporal pole	38	45	11	-20	3.51	
R insula	48	45	8	-8	3.39	
L cerebellum (culmen)	NA	-15	-46	-17	3.92	15/405
L posterior cingulate	23	-6	-16	37	3.86	16/432
L posterior cingulate	23	-15	-16	37	3.58	
L caudate	NA	-24	2	25	3.72	22/594
R postcentral gyrus	3	30	-22	40	3.65	11/297
L cuneus	18	-21	-76	1	3.49	10/270
Group (SZ > HC) x condition (NegInt vs. NegCon > NeuInt vs. NeuCon) interactions	No suprathreshold activity					

Note: Neural activity clusters are areas where NegInt-NegCon>NeuInt-NeuCon at $p < 0.001$ uncorrected with a cluster threshold of 10 voxels/270mm. Clusters that include cognitive control regions are italicized. Neuroanatomical labels, MNI coordinates, and t-values are provided for the peak voxel of each cluster. Where multiple peaks exist, primary peaks and cluster sizes are reported first and neuroanatomical labels and MNI coordinates of sub-clusters are shown indented. Regions indicated with a superscript survived small volume correction (FWE, $p < 0.05$) applied to our a priori regions of interest: (a) includes voxels in anatomically defined bilateral superior frontal gyri; (b) includes voxels in anatomically defined bilateral lateral orbitofrontal gyri.

Table 10. Bivariate Pearson correlations between LPFC activity during cognitive control of negative emotion and laboratory-based measures of symptoms and social functioning

	SAS Social & Leisure	**GFS Social**	**LH LPFC (BA46/9) [-39 20 40]**
Whole Group			
SAS Social & Leisure	-	**-0.79****	**-0.31***
GFS Social	-	-	0.20
HC Group			
SAS Social & Leisure	-	-0.26	0.03
GFS Social	-	-	-0.11
SZ Group			
SAS Social & Leisure	-	**-0.86****	**-0.52***
GFS Social	-	-	**0.47***
PANSS symptoms			
Positive	0.02	-0.07	0.05
Negative	**0.47***	**-0.45***	-0.16
Disorganized	0.03	-0.20	0.08
Excitement	-0.05	-0.08	0.03
Depression/Anxiety	0.12	-0.06	-0.28
Depression	0.28	-0.29	**-0.43***
Guilt	0.08	-0.06	-0.02
Anxiety	0.12	-0.12	-0.26
Somatic Concern	-0.15	0.29	-0.08

* $p < 0.05$; ** $p < 0.01$

Table 11. Daily diary variables, 21-day averages, and relationship to LPFC activation during cognitive control of negative emotion

Category	Mean (SD) [range]	α	F	*p*	*b*
Social Functioning					
Social Contact (yes/no)	2.55 (1.43) [0-6]	0.50	0.04	0.84	0.02
Prosocial Feelings	3.42 (0.42) [2.57-4.29]	0.62	7.03	**0.02***	0.08
Social Reward	3.93 (0.33) [3.27-4.40]	0.60	5.66	**0.03***	0.06
Conflict Occurrence [a] (yes/no)	0.58 (1.11) [0-7]	0.67	0.78	0.39	-0.05
Conflict Distress [b]	0.72 (1.28) [0-5]	-	0.55	0.47	-0.05
Anger during Conflict [b]	1.8 (0.83) [1-5]	0.60	2.62	0.12	-0.09
Avoidance During Conflict [b]	2.27 (0.95) [1-4]	0.50	4.35	**0.05***	-0.17
Conflict Resolution [b]	2.41 (0.94) [1-4.75]	-	11.03	**0.004****	0.23
Positive Symptoms					
Paranoia	2.11 (0.37) [1.75-3.05]	0.40	5.50	**0.03***	-0.07
Hallucinations/Odd Experiences	1.37 (0.58) [1-3.05]	0.71	1.26	0.28	-0.10
Negative Symptoms					
Amotivation	1.46 (0.64) [1-3.5]	0.28	0.28	0.60	-0.02
Disorganized Symptoms					
Disorganized Thinking	1.38 (0.47) [1-2.79]	0.77	2.27	0.15	-0.07
Mood					
Anxiety	1.50 (0.45) [1-2.60]	0.81	5.00	**0.04***	-0.08
Depression	1.46 (0.44) [1-2.71]	0.84	8.72	**0.008****	-0.09
Irritability	1.46 (0.43) [1-2.68]	0.82	5.25	**0.03***	-0.08
Positive Mood	2.49 (0.82) [1-4.75]	0.81	5.17	**0.03***	0.11
Neurocognition					
Cognitive Confusion	1.47 (0.47) [1-2.53]	0.63	5.52	**0.03***	-0.09

Note: Rating scale: 1 = not at all; 5 = extremely. See Supplemental Table 1 and Supplemental Table 2 for list of diary items. The dependent measure for each daily-diary variable was the average response from 1 to 5 diary questions. Table presents α for each daily-diary variable, and Fs, ps, and betas from HLM analyses investigating whether LPFC activity during cognitive control of emotion predicts daily social experiences in schizophrenia participants.

[a] Average number of conflicts over entire 21-day period = 11.55 (14.3) [0-46].

[b] Participants only responded to these questions when they had a conflict.

* $p < 0.05$. ** $p < 0.01$

Discussion

This study combines fMRI and experience sampling methods to investigate the relationship between neural mechanisms of cognitive control of emotional information and real-world social behavior in individuals with schizophrenia. Three key findings emerged. First, compared to healthy participants, individuals with schizophrenia showed lower LPFC activity during cognitive control of task-irrelevant negative emotional information. This is consistent with a large body of literature demonstrating LPFC dysfunction during cognitive control (Lesh, et al., 2011), specifically cognitive control of emotional information (Ursu, et al., 2011; Vercammen, et al., 2012). Second, schizophrenia participants showed deficient neural activity in cognitive control regions, including the superior frontal gyrus and lateral orbital gyrus, specifically when controlling emotional information on trials with the greatest cognitive demand (interference trials) suggesting that SZ participants' ability to control the influence of irrelevant negative emotional information on goal-directed behavior is only impacted during high load tasks. This is consistent with research demonstrating a relationship between LPFC dysfunction and task load (Callicott, et al., 2003), and further indicates that examination of cognition-emotion interactions is necessary to understand the role of emotion processing in the pathophysiology of schizophrenia. Third, in schizophrenia participants, LPFC activity during cognitive control of emotional information predicted daily-diary ratings of several aspects of social functioning. Lower LPFC activation during inhibition of irrelevant negative emotional information was associated with less prosocial feelings and enjoyment of social interactions, more avoidance during interpersonal conflicts, and less resolution of interpersonal conflicts. Analyses with laboratory-based measure of social functioning corroborated this relationship. These data provide the first evidence directly tying LPFC dysfunction in schizophrenia to daily ratings of real-world

social interactions and suggest that compromised LPFC function may be a vulnerability that contributes to social deficits via impaired cognitive control of emotional information.

This study adds to a growing body of research demonstrating that ecological measures of daily life can be combined with neuroimaging data to meaningfully connect neural indicators of psychological processes to real-world behavior (Berkman & Lieberman, 2011). In healthy individuals, LPFC activity predicts daily levels of social support (Eisenberger, Taylor, et al., 2007), successful smoking cessation (Berkman, et al., 2011), and maladaptive behavior following a conflict with a partner (Hooker, et al., 2010). Our findings extend this "brain-as-predictor" (Berkman, et al., 2011) approach to understanding the social consequences of well-established LPFC deficits in schizophrenia, and demonstrate the value of this approach to research attempting to delineate the mechanisms that contribute to social impairments.

This study also has substantive implications for understanding the specific role of LPFC dysfunction in social impairments in schizophrenia. Here, lower LPFC activation when inhibiting task-irrelevant negative emotional information predicted maladaptive social behavior (i.e. increased avoidance during social conflicts) and poorer quality of social interactions (i.e. reduced enjoyment of social interactions). This is consistent with evidence that adaptive response to social stressors requires LPFC control-related functions to regulate emotional information (Eisenberger, Gable, & Lieberman, 2007; Eisenberger, et al., 2003; Hooker, et al., 2010), and that prosocial behavior is reliant on self-control mechanisms (Telzer, Masten, Berkman, Lieberman, & Fuligni, 2011). Using a task that specifically assessed the interaction between cognitive control and emotion processing likely increased sensitivity to this brain-behavior relationship, and provides further support for the proposal that the social consequences of cognitive and emotion processing deficits in schizophrenia may be better understood in the

context of cognition-emotion interactions (Kring & Elis, in press; Pessoa, 2008). Furthermore, given that greater LPFC engagement during our laboratory-based measure of control of emotional information predicted better social functioning, interventions that aim to improve cognitive control of emotional information may also improve real-world forms of emotion control, and consequently, social functioning. Indeed, normalization of LPFC function has been shown to be related to symptom improvement (Edwards, et al., 2010) and treatment response (Kumari, et al., 2009). Our findings indicate that one mechanism by which normalization of LPFC activity translates into improved symptoms and social functioning may be improved cognitive control of emotional information.

Lower LPFC activity during cognitive control of negative emotional information also predicted higher daily ratings of depression, anxiety and irritability, and lower ratings of positive mood. This is consistent with evidence that hypoactivation in left LPFC relates to depression and reduced positive mood (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Hooker, et al., 2010) and suggests that the high prevalence of depressive symptoms among individuals with schizophrenia (Zisook, et al., 2006) may in part be due to impaired abilities to exert top-down control to down-regulate negative emotion. Lower LPFC activity in relation to symptoms of paranoia, although less intuitive, also fits within this framework. The proposal, consistent with our prior research (Hooker, et al., 2011), is that impaired cognitive control could contribute to affective information exerting inappropriate influence on perceptions and judgments about others, subsequently contributing to paranoia. This is consistent with the notion that impaired LPFC function and accompanying deficits in top-down control over cognition and behavior is a basis for symptomatology and functional impairment in schizophrenia (Lesh, et al., 2011).

Our results provide initial evidence that LPFC deficits in cognitive control of emotional information directly contribute to real-world social impairments in schizophrenia. However, limitations must be acknowledged. Given that participants completed the daily-diary at the end of each day, the precise temporal relationship between social stressors and symptoms cannot be determined (i.e. do increased symptoms predict increased social conflict, or vice versa?). Additionally, because of our previous findings regarding predictive value of LPFC activity the current study focused specifically on the role of LPFC in social behavior. Next steps should investigate the contribution of other regions involved in cognitive control of emotional information (e.g. ACC, fronto-parietal connectivity) to social impairments.

Conclusion

This study integrates fMRI and experience sampling methods to demonstrate a direct link between LPFC dysfunction during cognitive control of emotional information and real-world social behavior in schizophrenia. Results indicate that LPFC dysfunction contributes to symptoms and social deficits via impaired cognitive control of emotional information. These findings provide insight into potential neural mechanisms that could be targeted in treatment to improve real-world social behavior in schizophrenia.

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Discussion and Conclusion

Summary of Findings

This dissertation presents three papers that reflect a systematic investigation of the contribution of impaired cognitive control processes to the pervasive and disabling social impairments in schizophrenia.

Paper #1 demonstrated that self-reported cognitive control, as measured by the Attentional Control Scale (ACS; Derryberry & Reed, 2002), partially mediated the relationship between individual differences in social anhedonia and social impairment. Social anhedonia - a traitlike disinterest in social contact and diminished capacity to experience pleasure from social interactions - is one of the strongest psychometric predictors of schizophrenia (Kwapil, 1998) and a core negative symptom of the illness. The relationship between high social anhedonia and increased social impairment, replicated in paper #1, is well documented in the literature; the finding that self-reported cognitive control mediates this relationship illuminates one of the mechanisms underlying the relationship between a core negative symptom of schizophrenia and social impairments.

Papers #2 and #3 sought to build on the behavioral findings in paper #1 and establish a relationship between cognitive control and social impairments at the neural level. Paper #2 used surface-based morphometry techniques to establish a direct connection between cortical surface abnormalities in the lateral prefrontal cortex, cognitive control, and role functioning impairments. Results were threefold: schizophrenia participants had thinner cortex in a region of the superior frontal gyrus compared to healthy controls; decreased cortical thickness in this region related to decreased role functioning across all participants; and performance on a category fluency task - our measure of cognitive control - fully mediated the relationship

between cortical thickness in the superior frontal gyrus and role functioning. Paper #2 extends prior literature by directly testing the proposal that the neurobiological indicators of schizophrenia affect clinical/behavioral aspects of the illness through neurocognitive processes, specifically, cognitive control. Interestingly, paper #2 did not demonstrate a relationship between group-related differences in cortical thickness and social functioning. We proposed this could be due to the possibility that social functioning may be more strongly related to prefrontal regions involved in affective processes, and that this relationship is mediated by cognitive control of emotional information.

Paper #3 built on the findings of papers #1 and #2 by examining the specific role of cognitive control in the context of emotional information. By combining functional MRI and experience sampling methods paper #3 established a relationship between lateral prefrontal dysfunction during cognitive control, specifically of emotional information, and daily social experiences in schizophrenia. As would be expected based on prior literature, schizophrenia participants showed reduced lateral prefrontal activation during cognitive control of negative emotional information. More interesting, however, is that the extent of lateral prefrontal activation during cognitive control of negative emotional information predicted symptom exacerbation and daily social experiences, including reduced prosocial feelings, increased avoidance during social conflict, and reduced resolution of a given conflict at the end of the day. Not only do the findings of paper #3 corroborate those of papers #1 and #2 by again demonstrating the contribution of LPFC mediated cognitive control processes to functional impairment, but they also provide the first evidence directly tying LPFC dysfunction in schizophrenia to ecological assessment of real-world social interactions.

Implications

The findings in papers # 1 and #3 are consistent with the proposal that cognitive control is a domain general mental operation that effects social functioning through multiple higher level processes. In this model, cognitive control can be thought of as the foundation of a social functioning "building block" upon which higher-level processes necessary for successful social interactions are built. This model is compatible with the idea that neurocognitive impairments effect functioning via social cognitive impairments (Green, Kern, Braff, & Mintz, 2000), and is supported by the data herein.

In paper #1, cognitive control was shown to be a proximal mediator between social anhedonia and social impairment, indicating that cognitive control impacts social functioning through additional processes. Paper #3 demonstrates that one such process is cognitive control of affective information, specifically negative. However, given that cognitive control mechanisms are not just involved in inhibitory, but also facilitatory processes (e.g. generation and maintenance of goal representations) (Miller, 2000), impaired engagement of cognitive control mechanisms to down-regulate negative affective information could be accompanied by a complimentary deficit in the up-regulation of positive affective information. This could be particularly informative in light of the "anhedonia paradox" (Pizzagalli, 2010), which refers to the finding that schizophrenia patients tend to report attenuated experience of positive emotional stimuli on retrospective self-report measures, but show comparatively normal responses to positive stimuli in the moment (Germans & Kring, 2000; Horan, et al., 2008; Kring & Moran, 2008). Failure to up-regulate positive emotion may underlie this anticipatory pleasure deficit (Cohen, Najolia, Brown, & Minor, 2011; Kring & Moran, 2008; Pizzagalli, 2010), and could contribute to associated reward/motivational impairments thought to contribute to negative

symptoms of anhedonia and avolition (Gold, Waltz, Prentice, Morris, & Heerey, 2008; Horan, et al., 2008). For example, research demonstrates that individuals with schizophrenia have an impaired ability to mentally represent the value of a future reward/pleasant event (Gold, et al., 2008). It seems intuitive that this representation failure would then impact motivation to seek out pleasurable activities; if an individual is unable to retrieve/generate a representation of positive experiences from previous social interactions, they will be less likely to choose to seek out social interactions in the future. Consistent with this proposed representational deficit, patients consistently show a preference for immediate rewards on gambling tasks, even if the delayed reward is larger (Heerey, Robinson, McMahon, & Gold, 2007). Importantly, the ability to choose a larger but deferred reward is reliant on the LPFC (Bjork, Momenan, & Hommer, 2009), suggesting a direct relationship between LPFC mediated cognitive control mechanisms and the ability to generate representations of future rewards. Thus, it is possible that impairments in lateral prefrontal cognitive control mechanisms also impact social functioning via an impaired ability to up-regulate positively valenced representations of the value of social contact, leading to motivational deficits and social anhedonia, and consequently, poor social functioning. Future investigations could examine the differential contribution of inhibitory and facilitatory mechanisms of cognitive control to social functioning impairments to delineate this further.

More broadly, the findings of this dissertation have implications for how future research can approach investigations of the underlying mechanisms of social impairments in schizophrenia. Papers #2 and #3 add to a growing body of literature linking neural indicators to the neurocognitive and clinical aspects of the illness (Minatogawa-Chang, et al., 2009; Takizawa, et al., 2008; Zierhut, et al., in press), bridging the gap between neuroscience research and behavioral outcomes (Berkman & Lieberman, 2011). In particular, paper #3 demonstrates the

utility of the "brain-as-predictor" approach (Berkman, et al., 2011) by meaningfully connecting neural indicators of mental processes (i.e. LPFC dysfunction during cognitive control of emotion) to experience sampling data describing real-world behavior (i.e. social interactions and conflicts). The combination of neuroimaging and experience sampling methods (ESM) will likely be key to furthering our understanding of the neural underpinnings of behavioral and clinical phenotypes in schizophrenia. This may be particularly important for understanding social functioning because many of the important aspects of social interactions (e.g. social conflict) cannot be realistically reproduced in laboratory settings, let alone in the solo environment of an MRI scanner. Thus, ESM provides an ecologically valid method for examining the nature of social interactions in daily life that can be used to compliment experimental measures of the neural and cognitive mechanisms thought to be involved. ESM is by no means new to psychosis research; important contributions to our understanding of daily life functioning in schizophrenia have been made in recent years using the technique. For example, ESM revealed that visual hallucinations were reported more frequently than auditory hallucinations (Delespaul, deVries, & van Os, 2002), delineated anticipatory and consummatory pleasure processes in patients with social anhedonia (Gard, et al., 2007), and illuminated the nuanced relationship between person-environment interactions and symptom fluctuations (Oorschot, et al., 2009). Research in healthy individuals clearly demonstrates the value of combining neuroimaging and ESM data for understanding social behavior: LPFC activity has been shown to predict daily levels of social support (Eisenberger, Gable, et al., 2007), successful smoking cessation (Berkman, et al., 2011), and response to social conflict (Hooker, et al., 2010). By extending this methodology to research in schizophrenia samples, paper #3 makes a novel contribution to the literature and demonstrates that this type of research design is feasible in patient populations.

Limitations

This dissertation provides clear evidence that impairments in cognitive control and associated neural abnormalities in the LPFC contribute to social functioning deficits in schizophrenia. However, limitations must be acknowledged. Because of the proposal that LPFC dysfunction is a biomarker for schizophrenia (Lesh, et al., 2011; Woodward, et al., 2009), and previous findings regarding the predictive value of LPFC activity in understanding social behavior (Hooker, et al., 2010), this dissertation focused specifically on the contribution of the LPFC to social impairments. However, evidence clearly demonstrates dysfunctional activity in other components of the cognitive control network (e.g. the ACC; Harrison, et al., 2007) in schizophrenia, as well as aberrant connectivity within the network (Sanz, et al., 2009; Yoon, et al., 2008). Future investigations should examine the differential contribution of the components of the cognitive control network to social impairments.

Additionally, it is important to note that these findings cannot establish the causal direction with respect to the development of LPFC abnormalities and social deficits because of their cross-sectional design. Although paper #3 presents prospective data that illustrates LPFC dysfunction is predictive of social behavior three weeks later, the data cannot speak to the question of which came first. Here, the working model, rooted in prior literature, is that LPFC abnormalities are a genetically determined characteristic of schizophrenia (Cannon, et al., 2002; Oertel-Knöchel, et al., 2012) that contribute to deficits in cognitive control which in turn contribute to the development and maintenance of social impairments. However, it is possible that there is a feedback loop wherein stress from social deficits and other life events adversely impact LPFC structure and function, which in turn contribute to the maintenance of social impairments (Lupien, McEwen, Gunnar, & Heim, 2009). Only longitudinal studies in which

neural development, neurocognitive abilities, and social abilities are tracked over the life span can truly determine causal priority.

Conclusion

This dissertation presents a systematic investigation of the contribution of cognitive control deficits to social functioning impairments at both behavioral and neural levels. Findings show that (1) cognitive control mediates the relationship between social anhedonia and social impairments, (2) reduced cortical thickness in the lateral prefrontal regions relates to role functioning impairment, and this relationship is mediated by cognitive control, and (3) lateral prefrontal dysfunction during cognitive control, specifically cognitive control of emotional information, predicts daily social experience in schizophrenia. Results demonstrate a direct link between lateral prefrontal cortex abnormalities, a putative biomarker for schizophrenia, and one of the core behavioral characteristics of the illness - social impairments. These findings suggest that cognitive control, specifically of emotional information, could be a potential target for intervention to improve real-world social behavior in schizophrenia.

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Appendix

Supplemental Methods for Paper #3

Laboratory Assessments of Social Functioning. To corroborate our daily-diary findings, we administered two standard laboratory based measures of social functioning: the Global Functioning: Social scale (GFS; Auther, et al., 2006) and Social Adjustment Scale - Self-Report (SAS-SR; Weissman, et al., 1978). The SAS-SR consists of 54 questions assessing six major areas of functioning: work, social and leisure activities, relationships with extended family, role as marital partner, parental role, and role within the family unit. Areas of functioning are assessed across four categories: performance at expected tasks, level of conflict with people, interpersonal relations, and feelings and satisfactions. Area scores can be averaged to create a single composite score of social functioning. Given the focus on social functioning in the present study, we chose to use the area score for social and leisure activities. Higher scores on the SAS-SR represent greater social impairment. The GFS is a clinician rated assessment of social functioning using a 1 to 10 scale based on information gathered during clinical interviews; higher scores on the GFS reflect better functioning.

MSIT-Emotion Affective Picture Stimuli. Neutral pictures typically portrayed household objects including tables, chairs, and textiles; negative pictures included pictures of snakes, spiders, weapons, and interpersonal assault. Population means of valence and arousal ratings for these pictures, as reported in the IAPS manual, were as follows: the mean valence of negative pictures was 3.00 (SD = 0.91) and mean arousal was 6.29 (SD=0.58); the mean valence of neutral pictures was 4.96 (SD = 0.30) and mean arousal was 2.89 (SD= 0.57). Negative pictures were significantly more unpleasant ($t(94) = 14.297$, $p < 0.001$) and arousing ($t(94) = 29.030$, $p < 0.001$) than neutral pictures.

After the scan, 22 healthy participants and 20 schizophrenia participants rated the valence of each neutral and negative picture on a 7-point scale: -3 (extremely unpleasant) to extremely pleasant. Mean valence ratings for healthy participants: neutral pictures = 0.17 (SD=0.77); negative pictures = -1.80(SD=0.93). Mean valence ratings for schizophrenia participants: neutral pictures = 0.55 (SD=0.51); negative pictures = -1.77 (SD=0.61). There were no group differences in valence ratings of the neutral ($t(39) = -1.84$, $p = 0.73$) or negative pictures ($t(39)=-0.16$, $p=0.88$) indicating that schizophrenia and healthy participants experienced the affective stimuli as equally unpleasant.

fMRI Image Acquisition. Functional images were acquired with a 32 channel whole-head coil using a gradient echo T_2*-weighted echo planar sequence with parallel imaging (acceleration factor of 2; repetition time (TR), 2560ms; echo time (TE), 30ms; flip angle, 85 degrees). Each volume consisted of 47 contiguous slices acquired in the axial plane sequentially, in descending order (thickness, 3mm; gap, 0; field of view (FOV), 216mm x 216mm; matrix size, 72 x 72; voxel size, 3mm x 3mm x 3mm). Following functional image acquisition, a high resolution anatomical image was acquired for each subject using a 3-dimensional T1-weighted multi-echo magnetization-prepared rapid acquisition of gradient-echo (MEMPRAGE) sequence with parallel imaging (176 contiguous 1mm anterior commissure - posterior commissure slices; acceleration factor of 2; voxel size, 1 mm x 1 mm x 1 mm; flip angle, 7 degrees; TR, 2530 ms; TE, 7.22 ms; FOV, 256 mm x 256mm; matrix size, 256 x 256). Head movement was minimized using foam padding in the head coil and subjects wore earplugs to muffle scanner noise.

fMRI Image Processing. Images were acquired on a Siemens 3T Tim Trio scanner (Siemens Sonata, Erlangen, Germany) and analyzed using SPM8 within the general linear model (GLM) framework. (Wellcome Department of Cognitive Neurology, London, United Kingdom;

http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Image preprocessing included realignment to the first volume acquired, coregistration of anatomical and functional scans and transformation to standardized stereotaxic space (Montreal Neurological Institute template). Images were then smoothed with an 8mm full-width-half-maximum Gaussian kernel. All images were visually inspected for quality assurance by experienced neuroimaging analysts (LMT & CIH). Subjects with artifacts or abnormally low signal-to-noise ratio were excluded (1 HC; 1 SZ). When necessary, manual coregistration was conducted and preprocessing re-run. Artifact detection and movement correction was conducted using the Artifact detection tools software package (ART; Whitfield-Gabrieli, 2009). Regressors were created to exclude volumes with gross motion (>3mm relative to previous time frame) or spiking artifacts (global mean image intensity greater than 3SD from the mean of the entire time series within a scan) from analysis. Descriptives per group were as follows: HC mean = 10.54; SD = 7.71; range = 0 - 28; SZ mean = 10.52; SD = 8.11; range = 1 - 30.There were no group differences in number of outliers identified ($t(45) = 0.009$, $p = 0.993$).

Daily Diary Items. The daily diary consisted of a structured questionnaire completed online at the end of each day (i.e. 'right before bed') for 21 consecutive days. Diary questions focused on quality and quantity of social interactions, as well as schizophrenia-spectrum symptoms. The dependent measure for each daily-diary variable was the average response from 1-5 diary questions. Diary variables and included items are listed in Supplemental Table 1 and Supplemental Table 2 below.

Supplemental Tables for paper #3

Supplemental Table 1. List of social functioning diary variables and specific items included in each variable

Diary Variable: Social Functioning	Diary Items: Rating scale: 1 = not at all; 5 = extremely
Social Contact (yes/no)	I socialized with people online (e.g. email, facebook, chatrooms, etc.); I socialized with people on the phone (e.g. called an old friend to catch-up); I socialized with people during the course of my regular work, home life, or school day; I went to a party and socialized; I engaged in an interactive event with another person or group of people (e.g. played a game or participated in a team sport); I went out with another person (or small group) specifically to socialize (e.g. went out to lunch to talk, catch up on life events, and/or get to know someone better).
Prosocial Feelings	I felt accepted; I felt friendly; I felt lonely (reverse scored).
Social Reward	I socialized with other people and I enjoyed it; I socialized with other people and I felt like people liked me; I socialized with other people and wanted to get away and be by myself (reverse scored); I socialized with other people and I felt like a failure (reverse scored).
Conflict Occurrence (yes/no)	I felt attacked or threatened by someone else - verbally or physically; I felt that someone else was hostile towards me; I had a disagreement or distressing conversation with someone over a topic that was personally meaningful (e.g. sex, politics or religion); Someone ignored me or my request for something (e.g. asking a family member or roommate to turn off the TV); I felt manipulated or hurt by passive-aggressive behavior (e.g. my partner was late to an event that was important to me); Someone was critical of me or my behavior; Other people were over involved in my business and I wanted them to leave me alone.
Conflict Distress [a]	If yes, how distressing was this encounter?
Anger during Conflict [a]	During the encounter, I lost my temper or I did/said something hurtful to the other person; During the encounter, I was angry with the other person.
Avoidance During Conflict [a]	During the encounter, I refused to talk about the issue; During the encounter, I tried to bury my feelings to avoid further encounters.
Conflict Resolution [a]	At the end of the day, how well do you think the conflict/negative encounter was resolved?

[a] Participants only responded to these questions when they had a conflict.

Supplemental Table 2. List of schizophrenia-spectrum symptom diary variables and specific items included in each variable

Diary Variable: Symptoms	Diary Items: Rating scale: 1 = not at all; 5 = extremely
Positive Symptoms	
Paranoia	I felt that others dislike me; I felt that I had to be "on guard" with other people, even my friends; I felt trusting (reverse scored)
Hallucinations/Odd Experiences	I felt like my mind was playing tricks on me; I heard voices or whispers that didn't seem to be coming from anywhere identifiable; I had the experience of thinking I heard a sound and then realizing there was nothing there; I noticed unusual bodily sensations today, like tingling, pin pricks, burning, numbness, or pain that I do not usually have; I had the experience of seeing people, animals, or things, and then I realized they were not really there.
Negative Symptoms	
Amotivation	I felt like I didn't care about anything; I felt unmotivated and couldn't get things done
Disorganized Symptoms	
Disorganized Thinking	I had a hard time communicating thoughts and ideas to others; I had a hard time collecting my thoughts; I found myself going off-track or rambling a lot when I talked today.
Mood	
Anxiety	I felt anxious; I felt on edge; I felt uneasy
Depression	I felt sad; I felt hopeless; I felt discouraged; I felt depressed
Irritability	I felt angry; I felt resentful; I felt annoyed
Positive Mood	I felt cheerful; I felt vigorous; I felt lively; I felt happy
Neurocognition	
Cognitive Confusion	I felt confused; I felt distracted

Supplemental Table 3. MSIT-Emotion neutral interference effect related fMRI BOLD responses within groups

Region	BA	Peak MNI Coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
NeuInt vs. NeuCon - HC Group						
R vermis	NA	3	-67	-35	7.45	3932/106164
L Lingual gyrus	18	-12	-55	1	7.19	
R lingual gyrus	19	21	-55	4	7.03	
L cerebellum	NA	-18	-67	-44	5.76	36/972
L cerebellum	NA	-12	-61	-35	3.94	
R precentral gyrus	44	48	5	28	5.28	81/2187
*R inferior frontal gyrus**	48	36	14	19	4.45	
R insula	48	30	20	16	3.68	
R supplementary motor area	6	6	11	52	4.63	83/2241
*L anterior cingulate**	32	-6	11	46	4.26	
R supplementary motor area	6	9	2	67	3.65	
L precentral gyrus	44	-42	2	31	4.42	23/621
L cerebellum	NA	-27	-49	-50	4.28	19/513
L superior frontal gyrus[a]	6	-21	-7	52	4.24	46/1242
L superior frontal gyrus[a]	6	-27	-4	58	4.13	
R anterior cingulate	24	12	11	31	4.22	13/351
R posterior cingulate	23	6	-28	28	4.20	18/486
R posterior cingulate	26	6	-34	22	4.02	
L posterior cingulate	23	-3	-31	25	3.93	
L precentral gyrus	4	-36	-19	64	4.12	15/405
R inferior occipital gyrus	19	39	-88	-8	4.03	15/405
L insula	48	-36	17	4	3.89	15/405
NeuInt vs. NeuCon - SZ Group						
R insula*	48	33	20	7	7.87	215/5805
R insula*	48	48	11	-5	5.29	
R putamen*	48	33	-1	-2	3.91	
L superior parietal lobule*	7	-24	-61	49	6.27	1643/44361
L supplementary motor area*	6	-6	2	49	6.06	
L inferior parietal lobule*	7	-30	-55	52	5.69	
L cerebellum*	NA	-21	-49	-32	6.21	418/11286
L cerebellum*	NA	-33	-49	-35	5.92	
L fusiform gyrus*	37	-21	-46	-23	5.88	
*R superior frontal gyrus**	6	24	2	70	6.05	162/4374
*R superior frontal gyrus**	6	36	-4	61	4.21	

Supplemental Table 3.MSIT-Emotion neutral interference effect related fMRI BOLD responses within groups (Continued)

Region	BA	Peak MNI Coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
R fusiform gyrus*	37	24	-52	-20	5.92	335/9045
R fusiform gyrus*	19	24	-61	-17	5.15	
R fusiform gyrus*	19	36	-76	-17	5.06	
L inferior occipital gyrus	18	-30	-88	-11	5.91	93/2511
L middle occipital gyrus*	19	-39	-88	-5	4.82	
L middle occipital gyrus*	18	-30	-82	4	3.64	
R cerebellum	NA	24	-61	-47	5.70	38/1026
R cerebellum	NA	33	-55	-50	3.90	
R postcentral gyrus*	2	45	-40	61	5.04	143/3861
R inferior parietal lobule*	40	51	-34	58	4.45	
R inferior parietal lobule*	40	33	-40	46	4.44	
R superior parietal lobule*	7	24	-64	52	4.92	254/6858
R precuneus*	7	6	-61	55	4.43	
R precuneus*	7	9	-76	37	4.43	
L inferior frontal gyrus[b]	44	-54	8	28	4.90	37/999
R middle temporal gyrus	21	48	-46	-2	4.69	12/324
L middle frontal gyrus[c]	46	-39	41	34	4.63	17/459
L thalamus	NA	-12	-16	10	4.57	27/729
R inferior frontal gyrus	6	51	5	34	4.54	68/1836
R inferior frontal gyrus	44	39	5	34	3.65	
L insula	48	-33	17	10	4.50	27/729
L lateral orbital gyrus	47	-30	26	-2	3.83	
R middle frontal gyrus[d]	10	33	59	22	4.29	21/567
R lingual gyrus	19	21	-64	4	4.24	36/972
R lingual gyrus	19	24	-55	1	3.86	

Neural activity clusters are based on one sample t-tests (NeuInt>NeuCon) within each group with a significance threshold of $p< 0.001$ uncorrected and cluster threshold of 10 voxels/270mm. Clusters that include cognitive control regions are italicized. Neuroanatomical labels, MNI coordinates, and t-values are listed for the peak voxel of each cluster. Where multiple peaks exist, primary peaks and cluster sizes are reported first and neuroanatomical labels and MNI coordinates of sub-clusters are shown indented. Regions indicated with an asterisk survived whole brain correction for multiple comparisons (FWE, $p < 0.05$). Regions indicated with a superscript survived small volume correction (FWE, $p <0.05$) applied to our a priori regions of interest: (a) includes voxels in anatomically defined left superior frontal gyrus; (b) includes voxels in anatomically defined bilateral inferior frontal gyrus; (c) includes voxels in anatomically defined left middle frontal gyrus; (d) includes voxels in anatomically defined right middle frontal gyrus.

Supplemental Table 4. MSIT-Emotion negative interference effect related fMRI BOLD responses within groups

Region	BA	Peak MNI Coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
NegInt vs. NegCon - HC Group						
L inferior parietal lobule*	6	-27	-7	43	7.64	4673/126171
L supplementary motor area*	32	-9	8	46	6.91	
L hippocampus*	28	-21	-22	-11	6.75	
*R lateral orbital gyrus**	47	42	20	-8	6.73	332/8964
R insula*	48	39	14	-2	6.07	
R caudate*	NA	21	26	7	5.00	
L superior temporal gyrus*	22	-39	-46	10	6.43	130/3510
L middle temporal gyrus*	22	-30	-52	19	5.00	
L middle temporal gyrus*	21	-57	-49	7	4.73	
R inferior parietal lobule*	7	21	-46	46	6.22	304/8208
R postecentral gyrus*	40	27	-37	43	5.30	
R inferior parietal lobule*	7	27	-55	52	4.90	
L inferior temporal gyrus	37	-42	-34	-14	5.81	10/270
R cerebellum	NA	6	-61	-35	5.78	27/729
L calcerine fissure*	19	-21	-70	7	4.70	95/2565
L lingual gyrus*	19	-21	-58	4	3.65	
L cerebellum	NA	-15	-70	-38	4.60	46/1242
L cerebellum	NA	-15	-58	-47	4.60	
L cerebellum	NA	-6	-76	-35	3.97	
*R middle frontal gyrus**	6	33	-1	55	4.53	59/1593
*R superior frontal gyrus**	6	33	-1	70	4.25	
R calcerine fissure	17	21	-64	7	4.21	37/999
R thalamus	NA	12	-10	13	4.06	14/378
R thalamus	NA	9	-19	16	4.05	
R precentral gyrus	4	12	-25	73	3.93	16/432
NegInt vs. NegCon - SZ Group						
L inferior frontal gyrus	9	-57	5	31	5.56	84/2268
R superior temporal gyrus	48	69	-34	22	5.04	10/270
L middle frontal gyrus	6	-21	-7	49	4.71	
L precentral gyrus	6	-30	-10	52	3.59	
L inferior parietal lobule	40	-39	-43	64	4.50	63/1701
L postcentral gyrus	40	-39	-43	55	4.33	
L postcentral gyrus	40	-42	-37	40	3.69	

Supplemental Table 4. MSIT-Emotion negative interference effect related fMRI BOLD responses within groups (Continued)

Region	BA	Peak MNI Coordinates			t value	Cluster Extent (voxels/mm)
		x	y	z		
L precentral gyrus	6	-33	-16	64	4.09	44/1188
L precentral gyrus	6	-39	-28	70	4.00	
L postcentral gyrus	6	-45	-25	64	3.98	

Neural activity clusters are based on one sample t-tests (NegInt>NegCon) within each group with a significance threshold of $p< 0.001$ uncorrected and cluster threshold of 10 voxels/270mm. Clusters that include cognitive control regions are italicized. Neuroanatomical labels, MNI coordinates, and t-values are listed for the peak voxel of each cluster. Where multiple peaks exist, primary peaks and cluster sizes are reported first and neuroanatomical labels and MNI coordinates of sub-clusters are shown indented. Regions indicated with an asterisk survived whole brain correction for multiple comparisons (FWE, $p < 0.05$).